

In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

* * * * *

JOSEPH MICHAEL D'ANGIOLINI, *

Petitioner, *

v. *

SECRETARY OF HEALTH
AND HUMAN SERVICES, *

Respondent *

* * * * *

No. 99-578V

Special Master Christian J. Moran

Filed: March 27, 2014

hepatitis B vaccine; yeast allergy;
chronic fatigue syndrome ("CFS");
systemic lupus erythematosus
("SLE"); autoimmune syndrome
induced by adjuvants ("ASIA").

Barry W. Kregel, Dolchin, Slotkin & Todd, P.C., Philadelphia, PA, for petitioner;
Heather L. Pearlman, United States Dep't of Justice, Washington, DC, for
respondent.

PUBLISHED DECISION DENYING ENTITLEMENT TO COMPENSATION¹

Joseph D'Angiolini alleges that he experienced an adverse, and possibly allergic, reaction to the hepatitis B vaccination which caused him to develop chronic fatigue syndrome ("CFS"), systemic lupus erythematosus ("SLE"), and autoimmune syndrome induced by adjuvants ("ASIA"). Mr. D'Angiolini seeks compensation pursuant to the National Childhood Vaccine Injury Compensation Program, 42 U.S.C. §§ 300aa-10 through 34 (2012).

Mr. D'Angiolini primarily relies on the testimony of Dr. Frank Vasey, a board certified rheumatologist who has treated Mr. D'Angiolini since 2000, and

¹The E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (Dec. 17, 2002), requires that the Court post this decision on its website. Pursuant to Vaccine Rule 18(b), the parties have 14 days to file a motion proposing redaction of medical information or other information described in 42 U.S.C. § 300aa-12(d)(4). Any redactions ordered by the special master will appear in the document posted on the website.

Dr. Yehuda Shoenfeld, a specialist in autoimmune disease. In their testimony, Doctors Vasey and Shoenfeld discussed Mr. D'Angiolini's alleged injuries including CFS, SLE and ASIA. Mr. D'Angiolini's experts also provided various theories to explain how the hepatitis B vaccine could have caused Mr. D'Angiolini's alleged injuries. Mr. D'Angiolini's diagnoses and causation theories were opposed by respondent's expert witnesses: Dr. Robert W. Lightfoot, also a board certified rheumatologist, and J. Lindsay Whitton, PhD, who specializes in virology and immunology. For the reasons set forth below, Mr. D'Angiolini failed to establish persuasively that he does in fact suffer from any of his alleged injuries, including CFS, SLE and ASIA, and thus, has not demonstrated that he is entitled to compensation.

This decision is organized into the following topics:

Contents

I. Procedural History	2
II. Standards for Adjudication	16
III. Facts	17
IV. General Assessment of Witnesses	38
V. Yeast Allergy	45
VI. Chronic Fatigue Syndrome	51
VII. Lupus.....	75
VIII. ASIA.....	94
IX. Conclusion	100

I. Procedural History

This case is one of the oldest cases pending at the Office of Special Masters. This unusually lengthy procedural history certainly does not accord with the quick case processing Congress anticipated. See H.R.Rep. No. 99-908, reprinted in 1986 U.S.C.C.A.N. 6344, 6344. But, the amount of time for this litigation reflects an attempt to allow Mr. D'Angiolini to develop his case fully and persuasively.

Mr. D'Angiolini, represented by Clifford Shoemaker, filed his petition on August 4, 1999, alleging that the hepatitis B vaccine caused him to experience an adverse reaction. Pet., filed Aug. 4, 1999, at 1. Around this same time, Mr. D'Angiolini's mother sent a letter to her son's employer initiating a claim for

workers' compensation benefits. See exhibit 58 (decision of worker's compensation judge) at 4-5. The workers' compensation proceeding produced testimony from Mr. D'Angiolini's doctors, Mr. D'Angiolini, and Mr. D'Angiolini's mother.² Although the judge denied Mr. D'Angiolini's claim for workers' compensation benefits, exhibit 58 at 8, the outcome in that forum has played no role in the evaluation of the evidence in this case.

Early in the history of Mr. D'Angiolini's claim in the Vaccine Program, his case was included in a group of cases in which attorneys representing petitioners, attorneys from the government, and the Office of Special Masters were attempting to devise a procedure to expedite the resolution of numerous cases involving the hepatitis B vaccine. See Pet'r's Status Rep't, filed Feb. 15, 2000; Pet'r's Status Rep't, filed July 3, 2002 (requesting a stay); see also Hennessey v. Sec'y of Health and Human Servs., 91 Fed. Cl. 126 (Fed. Cl. 2010).

One approach was to organize cases by injuries. For example, cases in which the petitioners alleged that hepatitis B vaccine caused demyelinating diseases were treated similarly. See Peugh v. Sec'y of Health and Human Servs., No. 99-638V, 2007 WL 1531666 (Fed. Cl. Spec. Mstr. May 8, 2007) (hepatitis B vaccine caused Guillain-Barré syndrome); Werderitsh v. Sec'y of Health and Human Servs., No. 99-310V, 2006 WL 1672884 (Fed. Cl. Spec. Mstr. May 26, 2006) (hepatitis B vaccine caused multiple sclerosis); Gilbert v. Sec'y of Health and Human Servs., No. 04-455V, 2006 WL 1006612 (Fed. Cl. Spec. Mstr. Mar. 30, 2006) (hepatitis B vaccine caused Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy); Stevens v. Sec'y of Health and Human Servs., No. 99-594V, 2006 WL 659525 (Fed. Cl. Spec. Mstr. Feb. 24, 2006) (hepatitis B vaccine caused transverse myelitis).

² Mr. D'Angiolini collected the depositions of his treating doctors and filed them as one comprehensive exhibit, exhibit 50. Because there is no separate pagination within exhibit 50, this decision cites to the pdf pagination. In addition, a parenthetical identifies the page number of the specific deponent. For example, "Roman Dep. Tr. 16" refers to page 16 of the transcript for Dr. Roman's deposition.

Similarly, Mr. D'Angiolini and his mother testified before the workers' compensation judge on three days. He filed this set of transcripts as exhibit 51. A parenthetical specifies the date of the worker's compensation hearing. For example, "June 7, 2001 W.C. Trial Tr. 14" refers to page 14 of the transcript created on June 7, 2001 before the workers' compensation judge.

Mr. D'Angiolini's case became, for a period, the lead case to obtain a ruling whether the hepatitis B vaccine can cause chronic fatigue syndrome. See Pet'r's Status Rep't, filed Mar. 29, 2004; order, filed Apr. 2, 2004. The goal of Mr. Shoemaker was to identify experts who could testify at "a hearing on the general issue of causation, or the question of whether hepatitis B vaccination 'can' cause CFS." Pet'r's Status Rep't, filed June 16, 2004. Mr. D'Angiolini's counsel identified four doctors upon whom the petitioners intended to rely: Mark Geier, Harold T. Pretorius, Joseph A. Bellanti, and Carlo Tornatore. Pet'r's Status Rep't, filed Aug. 13, 2004.

In 2005, Mr. D'Angiolini's attorney worked to present reports from these doctors as well as two French doctors, Romain K. Gherardi and Marc Girard. Counsel explained that he was exploring whether components of the hepatitis B vaccine, including thimerosal, yeast, and aluminum in the adjuvant could contribute to an adverse reaction. Pet'r's Status Rep't, filed Mar. 14, 2005, at 3-4; Pet'r's Status Rep't, filed Apr. 19, 2005. By October 7, 2005, the list of potential experts had grown to eight (the six whom counsel had previously identified plus Charles Poser and Yehuda Shoenfeld). Pet'r's Status Rep't, filed Oct. 7, 2005.

On February 2, 2006, petitioner's counsel filed three reports into the D'Angiolini case file. These reports were written by Drs. Geier, Poser, and Shoenfeld. Exhibits 29-31.

The chief special master reassigned this case and six other cases involving chronic fatigue syndrome to the undersigned on February 21, 2006. A status conference to discuss the many cases involving the hepatitis B vaccine was held on March 27, 2006. In this status conference, it became apparent that an omnibus proceeding to address the claim that the hepatitis B vaccine can cause chronic fatigue syndrome was not needed. By this time, the number of cases involving the hepatitis B vaccine and chronic fatigue syndrome had decreased to a more manageable number of cases shifting the emphasis to develop the record for Mr. D'Angiolini's case specifically. See Pet'r's Status Rep't filed Oct. 7, 2005, table A (17 cases). Mr. D'Angiolini's attorney stated that he did not intend to reply upon opinions of Dr. Tornatore, Dr. Gherardi, or Dr. Girard.

After Mr. D'Angiolini filed all documents about his medical condition, the parties recognized apparent conflicts among the sources of information. See Resp't's Rep't, filed June 28, 2006, at 6-7. These inconsistencies led to a hearing

during which percipient witnesses testified about Mr. D'Angiolini's health.³ This process produced Findings of Fact, originally issued on April 29, 2010 and re-issued on May 18, 2010. This ruling primarily focused upon his health between 1996 (the year before Mr. D'Angiolini was vaccinated) and 1998 (the year after he was vaccinated).⁴

Because the April 29, 2010 Findings of Fact appeared to resolve the genuine issues of material facts, Mr. D'Angiolini sought an opinion from an expert that a dose of the hepatitis B vaccine harmed him. See 42 U.S.C. § 300aa—13(a)(1). Eventually, Mr. D'Angiolini filed reports from three experts, Yehuda Shoenfeld, Frank Vasey, and Harold Buttram.⁵ The Secretary filed reports from two experts, Robert W. Lightfoot, Jr. and Lindsay Whitton. All together, the parties submitted 15 reports from experts. These reports cited numerous articles, most of which the parties submitted as exhibits.

The first report came from Dr. Vasey, a rheumatologist who has treated Mr. D'Angiolini since 2000. In this report, Dr. Vasey stated that Mr. D'Angiolini “suffers from a rare Hepatitis B vaccine reaction which has permanently disabled him.” Dr. Vasey explained “the obvious explanation for Mr. D'Angiolini's reaction is the known yeast sensitivity documented at age 3 years.” Exhibit 83 at 4.

The next report was Dr. Shoenfeld's report.⁶ Dr. Shoenfeld specializes in the study of autoimmune diseases.

³ For reasons involving geography and schedules, the hearing was held in three separate sessions. The first session was on March 21, 2007, and the last session was on April 21, 2008. The transcript for this fact hearing (transcript pages 1-706), and the expert hearing which followed in January 2013 (transcript pages 707-1665) are cited in this decision as “Tr.”

⁴ The Findings of Fact describe the procedural events, including Mr. D'Angiolini's change of counsel, in more detail.

⁵ As discussed below, about one year after Mr. D'Angiolini filed Dr. Buttram's report, he withdrew it.

⁶ This chronology skips over the October 12, 2010 report from Dr. Shoenfeld that Mr. D'Angiolini mistakenly filed as exhibit 84. The October 12, 2010 report is obviously a draft and was not intended to be filed. Exhibit 87 at 1.

Dr. Shoenfeld reviewed Mr. D'Angiolini's medical history. He found that the hepatitis B vaccine "unleashed the emergence of [chronic fatigue syndrome], which then evolved into a clear cut diagnosed systemic lupus erythematosus." Exhibit 87 at 8.⁷ "Mr. D'Angiolini also fulfilled the criteria suggested by us for [autoimmune syndrome induced by adjuvants] syndrome." Id.⁸

In this report, Dr. Shoenfeld also addressed whether the onset of Mr. D'Angiolini's problems occurred within a time for which it was appropriate to infer that a vaccination caused the condition. Dr. Shoenfeld stated "in the past, to show a cause and effect of vaccine autoinflammatory reaction, we assumed that the period between the vaccine and the reaction has to be somewhere between 3 weeks . . . to 3 months. Better analysis of the cases of ASIA taught us that the period may extend to months or even years." Id. at 7.

On February 2, 2011, Mr. D'Angiolini filed a three-page supplemental report from Dr. Vasey. Dr. Vasey provided three theories to explain a possible causal connection between the hepatitis B vaccinations and Mr. D'Angiolini's injury. Exhibit 93.

These reports were discussed at a status conference. The Secretary indicated that she intended to obtain a responsive report.

The Secretary filed a report from Dr. Lightfoot, a rheumatologist. His report starts with a comprehensive description of Mr. D'Angiolini's medical history. Exhibit A at 4-14. Dr. Lightfoot goes on to question or to disagree outright with statements of Mr. D'Angiolini's experts. For example, Dr. Lightfoot quotes Dr. Shoenfeld as stating that Mr. D'Angiolini has a "clear cut diagnosed SLE," but Dr. Lightfoot asserts that Dr. Shoenfeld's statement is "simply a misstatement of fact. SLE is not the diagnosis of any other clinician." Exhibit A at 16, quoting exhibit 87 at 8.

⁷ The page numbers refer to the pagination centered at the top of the page.

⁸ In addition to chronic fatigue syndrome, systemic lupus erythematosus, and autoimmune syndrome induced by adjuvants, Dr. Shoenfeld's report briefly mentions fibromyalgia. Exhibit 87 at 11. Fibromyalgia is not relevant because Mr. D'Angiolini did not pursue a claim based upon fibromyalgia. See Pet'r's Suppl. Br., filed June 4, 2012.

Dr. Lightfoot emphasized that in 1996, which was before Mr. D'Angiolini was vaccinated, his obsessive compulsive disorder "was interfering with his care" and "his neuropsychiatric state was deteriorating before the vaccination." Exhibit A at 18. Dr. Lightfoot found "nothing to document a sudden change or worsening of petitioner's symptoms coincident with each vaccination." Id.

Dr. Vasey's next report challenged Dr. Lightfoot's representation that Mr. D'Angiolini did not change dramatically after his vaccination. Dr. Vasey wrote that Mr. D'Angiolini, "despite some psychological problems, functioned at a high level and was well liked at his job as a mental health technician and could play and teach guitar. Promptly after his hepatitis B vaccinations he could do neither." Exhibit 94 (report dated May 16, 2011) at 3.

Dr. Shoenfeld also responded to Dr. Lightfoot's April 27, 2011 report by writing a short report in which Dr. Shoenfeld cited 41 articles.⁹ Dr. Shoenfeld expressed a theory of what happened to Mr. D'Angiolini. "The adjuvant is chronically stimulating the immune system, thus leading to [an] avalanche of various autoantibodies, hyper-gamma globulinemia, and various clinical presentations characterized by severe fatigue . . . and neurological damage." Exhibit 95 (report dated May 30, 2011) at 2.

The next status conference was held on July 13, 2011. The parties discussed a June 7, 2011 order that had posed questions to Dr. Vasey and Dr. Shoenfeld and instructed Mr. D'Angiolini to obtain supplemental responses from them. The two recent reports (exhibits 94 and 95), although filed after the June 7, 2011 order, were actually written before June 7, 2011. When asked why Dr. Vasey and Dr. Shoenfeld did not address the questions in the June 7, 2011 order, Mr. D'Angiolini's attorney stated that he did not recall seeing the June 7, 2011 order and, therefore, had not sent the order to the experts. Thus, in the July 13, 2011 status conference, Mr. D'Angiolini was directed, again, to file supplemental reports from Dr. Vasey and Dr. Shoenfeld.

In addition, the parties started to plan for a hearing. The parties anticipated that the earliest mutually convenient dates would be in January or February 2012. In a subsequent status conference, the parties selected February 13-14, 2012. Orders, filed July 13, 2013 and Sept. 13, 2013.

⁹ Mr. D'Angiolini, however, did not file all the articles cited.

Mr. D'Angiolini filed the requested supplemental reports from Dr. Vasey and Dr. Shoenfeld on September 7, 2011. The questions posed to Dr. Vasey were primarily about his understanding of Mr. D'Angiolini's health. In response to those questions, Dr. Vasey stated "I agree with Dr. Lightfoot that at no time when I cared for [Mr. D'Angiolini] did he meet the criteria for lupus." Exhibit 96 at 1. Dr. Vasey stated that he did not know if Mr. D'Angiolini was allergic to yeast. Id. at 2. Dr. Vasey also indicated that "Mr. D'Angiolini suffers from an autoimmune condition in that he has chronic flu-like symptoms which clearly developed synchronously with his Hepatitis B vaccination." Id. at 3.¹⁰

Like Dr. Vasey, Dr. Shoenfeld also responded to the questions contained in the June 7, 2011 order. In response to a question about a yeast allergy, Dr. Shoenfeld stated "[t]he yeast allergy, if it exists, is not important for the claim of a long life [chronic fatigue syndrome] following the vaccine. . . . I believe that the case of the CFS [is] not due [to] yeast allergy but due to adjuvant effect." Exhibit 97 at 1. The adjuvant effect was part of Dr. Shoenfeld's answer to a question about elevated immunoglobulin levels. He stated that the adjuvant effect caused chronic stimulation of Mr. D'Angiolini's immune system and this chronic stimulation was manifest in high levels of immunoglobulins. Id. In another portion of his supplemental report, Dr. Shoenfeld stated that the adjuvant used in the hepatitis B vaccine, aluminum, was deposited into Mr. D'Angiolini's muscles, leading to macrophage myofasciitis and causing chronic fatigue. Id. at 3.

In addition, Dr. Shoenfeld responded to questions about Mr. D'Angiolini's diagnosis. Dr. Shoenfeld cited five medical records that supported the lupus diagnosis. He also cited four doctors who diagnosed Mr. D'Angiolini as having chronic fatigue syndrome. Exhibit 97 at 2.

Since Mr. D'Angiolini had filed four reports (two from Dr. Shoenfeld and two from Dr. Vasey), the Secretary had an obligation to disclose Dr. Lightfoot's response before any hearing. The Secretary submitted a supplemental report from him as exhibit R on October 6, 2011. In response to Dr. Vasey, Dr. Lightfoot

¹⁰ As discussed below, Mr. D'Angiolini pursues claims that he suffers from a yeast allergy, CFS, SLE and ASIA, but not an unspecified autoimmune condition as indicated in Dr. Vasey's report. Thus, Dr. Vasey's unspecified autoimmune theory is not discussed further. See Vaccine Rule 8(f)(1) (waiver of any fact or argument not raised specifically in the record before the special master).

noted a simple difference in opinion regarding Mr. D'Angiolini's health before and after vaccination. Exhibit R at 1.

For Dr. Shoenfeld, Dr. Lightfoot's response was more involved. Dr. Lightfoot questioned whether aluminum as an adjuvant in the vaccine could cause the harm as theorized by Dr. Shoenfeld. Dr. Lightfoot questioned the validity of the macrophage myofasciitis condition and did not understand how aluminum, which Dr. Shoenfeld said was deposited into muscles, could cause neurologic problems, like cognitive impairments. In addition, Dr. Lightfoot noted that Dr. Shoenfeld had not explained very well why he stated that Mr. D'Angiolini suffered from lupus, especially since Dr. Vasey had agreed that Mr. D'Angiolini did not suffer from lupus. Exhibit R.

Dr. Lightfoot's report dated October 4, 2011, was anticipated to complete the series of pre-trial reports. Thus, the undersigned issued a lengthy order, requiring the submission of briefs before the hearing. The purpose of the order was to afford the parties an opportunity to center their evidentiary presentations. This concentration would particularly assist Mr. D'Angiolini because, as the petitioner, he bore the burden of proof and because his attorney had not previously tried a case in the Vaccine Program. The order required Mr. D'Angiolini to set forth his evidence on each disputed element of his case, starting with the diagnoses and continuing through each of the three Althen prongs. See Althen v. Sec'y of Health & Human Servs. 418 F.3d 1274, 1278 (Fed. Cir. 2005); see also order, filed Oct. 27, 2011. Shortly after the order for pre-trial briefs, another order submitted into the record an article discussing aluminum compounds in vaccines as court exhibit 1001.

On December 22, 2011, Mr. D'Angiolini filed a two-page supplemental report from Dr. Shoenfeld with four articles. Exhibit 132. A more significant submission was Mr. D'Angiolini's pre-trial brief on January 5, 2012.

The January 5, 2012 brief presented Mr. D'Angiolini's view of his case. Primarily based upon the April 29, 2010 Findings of Fact, Mr. D'Angiolini summarized the relevant facts of his medical history. He asserted that within one week of the first dose of the hepatitis B vaccine, he was feeling "flu-ish." Pet'r's Br. at 2, citing Findings of Fact at 24. He made a similar assertion, regarding his reaction to the second dose. Id. Mr. D'Angiolini's brief also maintained that in the summer of 1997, he had "fatigue and overwhelming aches and pains." Pet'r's Br. at 2, citing Findings of Fact at 28.

In regard to the appropriate diagnosis for Mr. D'Angiolini, he claimed that he suffered from autoimmune syndrome induced by adjuvant, chronic fatigue syndrome, systemic lupus erythematosus, and fibromyalgia. Pet'r's Br. at 5. For ASIA, CFS, and lupus, Mr. D'Angiolini cited to some evidence in which medical records purportedly identified the sign or symptom fitting the relevant diagnostic criterion. Id. at 5-9.

For the medical theory causally connecting the hepatitis B vaccination to any injury suffered by Mr. D'Angiolini, his brief was relatively short. It covered this topic in a single paragraph, discussing the adjuvant. Based upon Dr. Shoenfeld's reports, Mr. D'Angiolini asserted:

[the] hepatitis B vaccine's adjuvant chronically stimulates the immune system, which causes the immune system to break its tolerance of its own constituents. The adjuvant can be deposited in the muscle, which disrupts muscle fiber, which causes fatigue. When adjuvant diffuses into the brain as nanoparticles, it causes damage to the brain cells, which leads to cognitive impairment, memory loss and other neurological manifestations.

Id. at 10.

For the logical sequence of cause and effect, Mr. D'Angiolini stated that he was relying upon Dr. Shoenfeld. In addition, Mr. D'Angiolini identified various doctors who linked his health problems to his hepatitis B vaccination. Id. at 11-12.

For the appropriate temporal relationship, Mr. D'Angiolini stated that Dr. Shoenfeld's report indicated that an autoinflammatory reaction can be anywhere from "weeks to months, even years." Mr. D'Angiolini also asserted that he "manifested [an] autoinflammatory reaction within one (1) week of receiving his first dose of Hepatitis B vaccine." Id. at 12, citing Findings of Fact at 24.

Finally, Mr. D'Angiolini presented his witness list. He included Dr. Shoenfeld, Dr. Vasey, and Dr. Harold Buttram. Id. at 13.

The day after Mr. D'Angiolini filed his pre-trial brief, he filed a 30-page report from Dr. Buttram. Exhibit 153. As alluded to earlier, Mr. D'Angiolini eventually withdrew this report. Hence, the details of Dr. Buttram's opinion are largely irrelevant to the outcome of the case. However, the submission of Dr. Buttram's report disrupted the progression of the case.

A status conference was held on January 9, 2012. Mr. D'Angiolini's attorney represented that he had not solicited Dr. Buttram's report. Rather, Mr. D'Angiolini's mother had contacted Dr. Buttram and obtained it. Mr. D'Angiolini's attorney stated that he told Mr. D'Angiolini and his mother that he would file the report, although it might delay the case. As Mr. D'Angiolini's attorney expected, the Secretary's attorney expressed concern about needing to respond to the report from a new expert so quickly.

The temporary solution was to divide the hearing. On February 12-13, 2012, Dr. Shoenfeld, Dr. Vasey, and Dr. Lightfoot would testify. On a different date, Dr. Buttram and an expert retained by the Secretary would testify. In light of this plan, the Secretary was instructed to respond to Mr. D'Angiolini's pre-trial brief, but to set aside Dr. Buttram's report temporarily. Order, filed Jan. 20, 2012.

The Secretary filed her pre-hearing brief on January 19, 2012. She disputed each of the four potential diagnoses Mr. D'Angiolini had proposed (ASIA, lupus, CFS, and fibromyalgia). Resp't's Br. at 5-8. As to the medical theory, the Secretary quoted the portion of Mr. D'Angiolini's brief quoted above. The Secretary argued that Dr. Shoenfeld's adjuvant-based theory was not reliable. Id. at 16-17. For the logical sequence of cause and effect, the Secretary emphasized that many of Mr. D'Angiolini's problems appeared before the hepatitis B vaccinations. Immediately after the vaccinations, Mr. D'Angiolini did not experience any adverse reaction. Id. at 17, citing Findings of Fact at 25-29.

For the proximate temporal relationship, the Secretary also challenged Mr. D'Angiolini's proof. The Secretary stated "Dr. Shoenfeld opined that the earliest onset time for [an autoinflammatory] reaction is three weeks." Id. at 19, citing exhibit 87 at 7. Mr. D'Angiolini's brief argued that he had "manifested autoinflammatory reaction within one (1) week of receiving his first dose Hepatitis B vaccine." Id., quoting Pet'r's Br. at 12. Thus, according to the Secretary, Mr. D'Angiolini's claim "would be too soon to have been vaccine-related." Id.

After the Secretary's brief, Mr. D'Angiolini filed 19 articles, exhibits 155-73. Although all discussed ASIA, Mr. D'Angiolini did not submit an expert report explaining the significance of those articles.

A lengthy pre-trial conference was held on February 1, 2012. Three topics dominated the discussion. First, the Secretary questioned whether she was given adequate notice of the newly filed articles. Second, Mr. D'Angiolini's version of his medical history was inconsistent with the Findings of Fact on the important

topic of his health in the days immediately after the hepatitis B vaccinations. For example, while Mr. D'Angiolini cited to page 24 of the Findings of Fact for the proposition that he felt "flu-ish" after the second dose of the vaccine, this portion of the findings of fact merely presented Mr. D'Angiolini's claim. However, his claim was not accepted. The next paragraph begins "[a] preponderance of the evidence does not support a finding that Mr. D'Angiolini was feeling flu-ish." This discrepancy jeopardized Mr. D'Angiolini's claim because if his symptoms were fundamental to his expert's opinion, then his expert's opinion could not be accepted. See Burns v. Sec'y of Health & Human Servs., 3 F.3d 415 (Fed. Cir. 1993).

The third topic at the February 1, 2012 pre-trial conference was the timing prong from Althen. As the Secretary argued in her pre-trial brief, Mr. D'Angiolini's case did not add up correctly. Dr. Shoenfeld stated that the minimum amount of time for a vaccine autoinflammatory reaction was three weeks. Exhibit 87 at 7. Yet, Mr. D'Angiolini stated he felt flu-ish only one week after the vaccination. Pet'r's Br. at 10. The undersigned explained in the pre-trial conference that if Mr. D'Angiolini's evidence were credited, he would not prevail because he could not establish the third prong of Althen. See Bazan v. Sec'y of Health & Human Servs., 539 F.3d 1347, 1352 (Fed. Cir. 2008).

Under these circumstances, Mr. D'Angiolini requested a suspension of the hearing and his request was granted. The Secretary was given a deadline for Dr. Lightfoot's next supplemental report to respond to the recently filed articles about ASIA. The Secretary was also given a deadline to submit an initial report from Lindsay Whitton, who was responding to Dr. Buttram's report.

The Secretary filed Dr. Whitton's report on March 15, 2012, as exhibit V. Because his report responded to Dr. Buttram's report, which was later withdrawn, most of Dr. Whitton's comments do not affect the outcome of the case. The Secretary, however, has not withdrawn Dr. Whitton's report and he offered a small amount of testimony at the hearing. See Tr. 1594-662.

The next two reports from experts concerned ASIA. Dr. Lightfoot's March 19, 2012 report appears as exhibit II. Dr. Lightfoot criticized ASIA, saying "the criteria are so non-specific as to make it unclear whether ASIA is a syndrome at all. It is my feeling that ASIA remains a hypothesis until such time as its proponents can validate their criteria and sharpen them quantitatively." Exhibit II at 3.

Dr. Shoenfeld had a chance to respond. Unfortunately, some (but not all) of Dr. Shoenfeld's criticisms attacked Dr. Lightfoot on a personal level. Exhibit 188.

The final expert report was written by Dr. Shoenfeld to address the temporal relationship. Dr. Shoenfeld's theory was that the adjuvant in a vaccine can cause "chronic and persistent stimulation of the immune system." Exhibit 189 at 2. Differences in number of vaccinations, in the interval between vaccinations, and in the type of vaccinations contribute to a variable development of problems. Dr. Shoenfeld stated "the first signs or symptoms and lab results . . . will be seen progressively and sometimes after months and even years." Id. at 3.

Dr. Shoenfeld did not specify when Mr. D'Angiolini's problem began, although Dr. Shoenfeld listed a series of events, spanning from 1997 to 2004, in his report. Exhibit 189 at 4-7. Dr. Shoenfeld did assert that "[a]ny initial reactions experienced by Mr. D'Angiolini should be considered allergic reactions as a result of his allergy to yeast." Id. at 4.

Having received these supplemental reports from Dr. Shoenfeld, Mr. D'Angiolini incorporated many of these ideas into his supplemental pre-trial brief filed on June 4, 2012. The Supplemental Brief contained some alterations in most of Mr. D'Angiolini's case, except for the section regarding Althen prong two. In regard to any assertions in the January 5, 2012 brief that were not consistent with the Findings of Fact, Mr. D'Angiolini "expressly rescinded" them. Pet'r's Suppl. Prehr'g Br. at 1 n.1; accord id. at 12 n.6. Unlike the January 5, 2012 brief that had put forward four conditions, the June 4, 2012 brief advanced three --- ASIA, lupus and CFS. Id. at 2-5.¹¹

Although the brief attempted to identify medical records that indicated Mr. D'Angiolini suffered from signs or symptoms related to ASIA, lupus, and CFS, the significance of many citations was unclear. For example, petitioner referred to a letter from Dr. Black dated March 29, 1999 (exhibit 9 at 2) as evidence for fulfillment of a minor ASIA criteria described as "[t]he appearance of autoantibodies or antibodies directed at the suspected adjuvant." Pet'r's Suppl. Prehr'g Br. at 3. Although Dr. Black's letter indicated an increase in gammaglobulins, there is no indication that these immunoglobulins were of a type

¹¹ In a June 12, 2012 status conference, Mr. D'Angiolini's attorney confirmed that he intentionally withdrew the claim that Mr. D'Angiolini suffered from fibromyalgia.

directed at the suspected adjuvant. Mr. D'Angiolini also referred to a record from Dr. Buttram as evidence of arthralgia and arthritis where no joint or arthritic pain was indicated. Pet'r's Suppl. Prehr'g Br. at 2, citing exhibit 14 at 4.

The June 4, 2012 brief expanded the theory causally connecting the hepatitis B vaccinations to any of these conditions. In this brief, Mr. D'Angiolini's attorney asserted that the

Hepatitis B aluminum adjuvant . . . chronically stimulates the immune system, which causes the immune system to break its tolerance to its own constituents. The chronic and persistent stimulation of the immune system by the adjuvant causes the expression of diverse clinical manifestations. . . . Here they were diagnosed as ASIA, CFS and/or Lupus[-]like symptoms.

Pet'r's Suppl. Prehr'g Br. at 7-8.

A final change concerned the temporal relationship, which corresponds to Althen prong 3. Mr. D'Angiolini asserted that "the autoinflammatory reaction can be seen, in terms of time between receiving the initial hepatitis B vaccination and the subsequent 'boost injections,' within weeks to months of the ultimate diagnosis of an autoimmune reaction." Pet'r's Suppl. Prehr'g Br. at 12.

The parties discussed Mr. D'Angiolini's Supplemental Brief in a status conference on June 12, 2012. The most significant substantive topic was whether the evidence cited in support of a diagnosis actually supported the diagnosis. In this respect, the Secretary contemplated filing a motion for summary judgment with respect to the claim that Mr. D'Angiolini suffered from lupus, although the Secretary eventually declined to pursue this motion.

The discussion about the proper diagnosis prompted Mr. D'Angiolini to file another submission. Although submitted as "exhibit 191," this document is more like a brief in that Mr. D'Angiolini's attorney argued why identified medical records support a diagnosis. Exhibit 191 was more effective and more persuasive than either Mr. D'Angiolini's January 5, 2012 brief or his June 4, 2012 supplemental brief.

The efforts to reschedule the hearing for mutually convenient dates culminated in a June 27, 2012 scheduling order, setting the case for a hearing from January 14, 2013 to January 18, 2013. The parties planned to have Dr. Shoenfeld,

Dr. Vasey, and Dr. Lightfoot testify for the three days. Dr. Buttram and Dr. Whitton would testify on the final two days.

Between June 27, 2012 and the next pre-trial conference, which was held on January 3, 2013, there was relatively little activity. Mr. D'Angiolini was awarded approximately \$200,000 in attorneys' fees and costs on an interim basis. Decision, filed July 18, 2012. The undersigned submitted two more exhibits into the record. Order, filed July 20, 2012. The parties reported that efforts to settle the case were not successful. Pet'r's Status Rep't, filed Nov. 1, 2012.

Once it appeared certain that the case was proceeding to hearing, the undersigned submitted two additional medical articles into the record. Order, filed Jan. 9, 2013. These articles concerned whether yeast in the hepatitis B vaccine can cause an adverse reaction. Exhibits 1004-05. The parties were alerted to have their experts prepared to testify about these articles.

The hearing began on January 14, 2013, when Mr. D'Angiolini called Dr. Shoenfeld to testify. Dr. Shoenfeld generally testified in accord with his reports. But, Dr. Shoenfeld also presented articles that he had not cited and had not been filed into the record. The Secretary objected because the October 2, 2012 order for pretrial submissions restricted the discussion of articles that had not been filed into the record. Tr. 777-86.

After Dr. Shoenfeld's testimony, Dr. Lightfoot testified. His testimony, too, mostly tracked what he had stated in his reports. The next witness was Dr. Vasey, who appeared via videoconferencing. Dr. Vasey completed his testimony on January 16, 2013.

When these witnesses were testifying, Mr. D'Angiolini was attempting to arrange for Dr. Buttram to testify, as scheduled, on January 17, 2013. Mr. D'Angiolini's attorney eventually learned that Dr. Buttram could not participate for reasons that could not be solved with a simple postponement of his testimony. Consequently, Mr. D'Angiolini withdrew Dr. Buttram's report entirely. While the Secretary acceded to the withdrawal of Dr. Buttram's report, the Secretary maintained that she still intended to call Dr. Whitton to address some aspects of Dr. Shoenfeld's testimony. Tr. 1591-93.

Dr. Whitton was the final witness and he testified on January 17, 2013. He addressed allergy and whether Mr. D'Angiolini was allergic to yeast. Tr. 1594-1662.

After the hearing concluded, the parties chose to submit briefs. Mr. D'Angiolini filed a primary brief, the Secretary filed one brief, and Mr. D'Angiolini filed a reply brief. With the submission of Mr. D'Angiolini's reply brief, the case is ready for adjudication.

II. Standards for Adjudication

Petitioners are required to establish their cases by a preponderance of the evidence. 42 U.S.C. § 300aa-13(1)(a). The preponderance of the evidence standard requires a “trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence.” Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010) (citations omitted). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991).

Distinguishing between “preponderant evidence” and “medical certainty” is important because a special master should not impose an evidentiary burden that is too high. Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1379-80 (Fed. Cir. 2009) (reversing special master's decision that petitioners were not entitled to compensation); see also Lampe v. Sec'y of Health & Human Servs., 219 F.3d 1357 (2000); Hodges v. Sec'y of Health & Human Servs., 9 F.3d 958, 961 (Fed. Cir. 1993) (disagreeing with dissenting judge's contention that the special master confused preponderance of the evidence with medical certainty).

Mr. D'Angiolini has established, by a preponderance of the evidence, most of the elements set forth in 42 U.S.C. § 300aa-11(c), including that he received a vaccine listed on the Vaccine Table, the hepatitis B vaccine. The disputed issue is whether the hepatitis B vaccine caused Mr. D'Angiolini an injury.

Here, the parties dispute whether Mr. D'Angiolini suffered any injury for which he seeks compensation. In this circumstance, Mr. D'Angiolini bears the burden of establishing that he suffers from a condition for which he seeks compensation. Broekelschen v. Sec'y of Health & Human Servs., 618 F.3d 1339, 1346 (Fed. Cir. 2010), Lombardi v. Sec'y of Health & Human Servs., 656 F.3d 1343, 1352 (Fed. Cir. 2011) (“under Broekelschen, identification of a petitioner's injury is a prerequisite to an Althen analysis of causation”). In doing so, the special master is “not ‘diagnosing’ vaccine-related injuries.” Knudsen v. Sec'y of Health & Human Servs., 35 F.3d 543, 549 (Fed. Cir. 1994). Rather, the special master evaluates the evidence presented and determines whether the petitioner has

met his burden of establishing that he suffers from the disease. See Lombardi, 656 F.3d at 1353-56 (reviewing evidence that the special master considered in determining whether petitioner suffered from a particular disease and finding that the special master's factual findings were not arbitrary or capricious).

After petitioners establish that they suffer from a particular condition, they must establish that the vaccine caused that injury. For causation-in-fact claims, the Federal Circuit set forth a three-prong test. Althen, 418 F.3d 1274.¹² To receive compensation, a petitioner must satisfy the Althen test by a preponderance of evidence. The preponderance of evidence standard is also used for finding facts about Mr. D'Angiolini's health.

III. Facts

A. Health before First Dose of Hepatitis B Vaccination

Mr. D'Angiolini was born in 1966. Tr. 143. When he was approximately 11 or 12 years old, Mr. D'Angiolini had the first symptoms of obsessive compulsive disorder ("OCD"), and was later diagnosed with that disorder. Exhibit 24 at 5-7. A psychologist provided some counseling to him as an adolescent, although the psychologist was primarily seeing Mr. D'Angiolini as part of her work in counseling a member of Mr. D'Angiolini's family. Tr. 88, 108. Mr. D'Angiolini's OCD did not prevent him from graduating from high school. He entered college but did not graduate. Exhibit 16 at 14; Tr. 660.

When he was approximately 20 years old, he started developing headaches three or four times a week. Exhibit 24 at 6. In August and September 1996, Mr. D'Angiolini was experiencing headaches three or four times per week and his OCD behaviors were intensifying. Dr. Debra Roman prescribed Fioricet for his headaches. Exhibit 23 at 35-36; exhibit 50 pdf 255 (Roman Dep. Tr. 16); Tr. 665-68.

However, in August and September 1996, Mr. D'Angiolini's physical health was otherwise fine. Blood tests were normal. Exhibit 23 at 99-102. He played

¹² Section VI.D presents the Althen test in more detail.

basketball and rollerbladed. Exhibit 51 pdf 26 (June 7, 2001 W.C. Trial Tr. 14); Tr. 93.

Mr. D'Angiolini was working two jobs. He worked at Pottstown Medical Center as a technician for mental health patients. Tr. 150-51, 409-11. He also worked part-time as a music instructor at Bachman's Music Store, earning about \$100 per week. Exhibit 16 at 296-301.

On the other hand, Mr. D'Angiolini's mental health was not good. His psychologist, Nancy Casella, referred him to a psychiatrist, Dori Middleman, because Mr. D'Angiolini's OCD symptoms were increasing and were disruptive to his relationship with his fiancée. The psychologist anticipated that Dr. Middleman would prescribe medications to help Mr. D'Angiolini. Exhibit 56 at 2; Tr. 98; see also Tr. 319, 480-81, 665-69.

The first appointment between Dr. Middleman and Mr. D'Angiolini occurred on October 29, 1996. Mr. D'Angiolini was having headaches that were causing him either to arrive late for work or to miss work entirely. Dr. Middleman diagnosed him as having OCD with a sexual compulsion and prescribed Prozac. Exhibit 24 at 5-7; Tr. 6-17.

Mr. D'Angiolini continued to see Dr. Middleman throughout the remainder of 1996, with both in-person and telephone consultations. Mr. D'Angiolini continued to have headaches and Dr. Middleman added another medication, amitriptyline. Exhibit 24 at 7-8.

In January 1997, Mr. D'Angiolini found a new job as a mental health technician at Valley Forge Medical Center. After a pre-employment physical examination, he was found capable of performing the job's duties. Exhibit 16 at 174, 176-78; exhibit 51 at pdf 17 (June 7, 2001 W.C. Trial Tr. 5).

Around this time, Mr. D'Angiolini's engagement was ending. He was both sad and relieved about its end. Tr. 223, 338, 484; exhibit 56 at 2; see also exhibit 24 at 9; exhibit 51 at pdf 153 (May 31, 2002 W.C. Trial Tr. 15); Tr. 544-45. In February 1997, Mr. D'Angiolini told Dr. Middleman that he was having difficulty sleeping and attributed the problem to the end of his engagement. Dr. Middleman stopped amitriptyline and prescribed a different drug, trazodone. Two weeks later, Mr. D'Angiolini was having less anxiety. Exhibit 24 at 9-10; Tr. 24-25.

Mr. D'Angiolini started working at Valley Forge Medical Center on March 3, 1997. Exhibit 51 at pdf 190 (May 31, 2002 W.C. Trial Tr. 52); exhibit 16 at 37.

In the context of his employment, he received his first dose of the hepatitis B vaccine on March 18, 1997. Exhibit 16 at 162, 233; Tr. 569-570.

B. Condition from March 18, 1997, the date of the first dose of the hepatitis B vaccination, through October 24, 1997, the date of the third dose of hepatitis B vaccine.

In the days immediately following the March 18, 1997 hepatitis B vaccination, Mr. D'Angiolini continued to work at Valley Forge. Tr. 231-32. His employment records show that between March 14, 1997 and March 27, 1997 (two weeks), he worked 81 hours. Exhibit 16 at 93. His employment records do not show that he missed work due to sickness during these two weeks, but do show absences due to illnesses at other times. See exhibit 16 at 179-80. His performance as a mental health technician met his employer's standards. Id. at 31 (evaluation covering March 3, 1997 through May 31, 1997). In the week following March 18, 1997, Mr. D'Angiolini also saw 15 students at Bachman's Music Store. Exhibit 16 at 304. Mr. D'Angiolini did not establish that he was "flu-ish" a few days after the first vaccination. See Findings of Fact at 22 n.9.

On April 18, 1997, Mr. D'Angiolini received the second dose of the hepatitis B vaccine. Exhibit 16 at 162, 233; Tr. 236, 590. Again, in the days and weeks immediately following this immunization, he maintained his employment. See exhibit 16 at 263 (Valley Forge), 305-07 (Bachman's Music Store); see also Tr. 596-600. Mr. D'Angiolini failed to establish that he was experiencing flu-like symptoms after this vaccination. See Findings of Fact at 23.

In May 1997, Mr. D'Angiolini was sleeping 15 hours a day and drinking coffee to stay awake at work. Exhibit 24 at 11 (Dr. Middleman's notes from May 22, 1997); exhibit 51 at pdf 193 (May 31, 2002 W.C. Trial Tr. 55). He was having headaches that were more severe, and that he described as migraines. Exhibit 24 at 11; exhibit 51 at pdf 49 (June 7, 2001 W.C. Trial Tr. 37).

Following Mr. D'Angiolini's visit with Dr. Middleman on May 22, 1997, he did not see her again until September 22, 1997. In this interlude, Mr. D'Angiolini had one visit with a doctor, Joshua Bray, on July 29, 1997.¹³ Mr. D'Angiolini

¹³ Mr. D'Angiolini also saw Dr. Bray after he developed more severe problems in November 1997. Because of Mr. D'Angiolini's reliance on Dr. Bray's records, additional (...continued)

reported that he had “nasal stuffiness, AM bloody/yellow discharge.” Dr. Bray diagnosed a sinus infection and prescribed a medication. Exhibit 61. Mr. D’Angiolini missed some days of work due to sinusitis in July and August 1997. Exhibit 16 at 175, 179-80. Throughout the summer 1997, Mr. D’Angiolini also taught music at Bachman’s. Exhibit 16 at 305-09; Tr. 613-15.

The Findings of Fact resolved a dispute over Mr. D’Angiolini’s health in the summer 1997. Although he maintained that he was fatigued during the summer, Joint Statement, filed October 19, 2009, at 11-12, the Findings of Fact did not credit this testimony. Mr. D’Angiolini did not seek medical attention for being fatigued and on the one occasion when he did seek medical care, Mr. D’Angiolini did not mention fatigue as a problem. Findings of Fact at 27.

On October 6, 1997, Mr. D’Angiolini saw Dr. Middleman and Mr. D’Angiolini told her that he was depressed. This was the first time Dr. Middleman noted “depression” for Mr. D’Angiolini. Exhibit 24 at 12; Tr. 62.

On October 24, 1997, Mr. D’Angiolini received his third dose of the hepatitis B vaccine. Exhibit 16 at 162, 233.¹⁴

C. Health after October 24, 1997, the date of the third dose of hepatitis B vaccine

On November 4, 1997, Mr. D’Angiolini requested an appointment with Dr. Middleman on an emergent basis. She saw him the next day. Mr. D’Angiolini stated he was sleeping 12-15 hours per day, not taking care of his apartment, and not tending to his appearance. He reported that he had returned to visiting prostitutes and was tempted to prostitute himself. Exhibit 24 at 13; Tr. 36, 75-76; see also exhibit 51 at pdf 164 (May 31, 2002 W.C. Trial Tr. 26). Dr. Middleman

information about Dr. Bray is presented in the context of the post-November 1997 treatment. See section III.C.1 below.

¹⁴ As discussed during the entitlement hearing, Tr. 712, the Findings of Fact contain an error in describing Mr. D’Angiolini’s health in the days immediately after he received the third dose of the hepatitis B vaccine. Although the factual findings state that Mr. D’Angiolini was fatigued by October 30, 1997, there is no persuasive evidentiary support for this finding. The undersigned therefore corrects this factual finding and finds instead that Mr. D’Angiolini was not fatigued in the weeks following this third vaccination.

recommended that Mr. D'Angiolini seek inpatient care for his sexual behavior at either the Keystone Center or Northwestern Institute. Exhibit 24 at 13; Tr. 36-37. Mr. D'Angiolini did not take her recommendation. Tr. 623.

November 5, 1997, was also the last date Mr. D'Angiolini worked at Valley Forge Medical Center. Exhibit 51 at pdf 20 (June 7, 2001 W.C. Trial Tr. 8); exhibit 53 ¶ 11. He stopped working because he was both mentally and physically incapable of taking care of himself. He was not showering or shaving. Exhibit 51 at pdf 20-21 (June 7, 2001 W.C. Trial Tr. 8-9). He began a leave of absence from Valley Forge the next day. Exhibit 16 at 118, 150. Mr. D'Angiolini's employment with Bachman's Music Store also terminated around this time. See exhibit 51 pdf 18, 40 (June 7, 2001 W.C. Trial Tr. 6, 28); exhibit 16 at 311.

1. Treatment with Dr. Bray in late 1997 and early 1998

On November 6, 1997, Mr. D'Angiolini saw Dr. Bray. As mentioned earlier, see footnote 12 above, Dr. Bray's later records are a primary basis for many of Mr. D'Angiolini's claims, particularly with respect to Mr. D'Angiolini's assertion that he suffers from lupus. The Secretary, however, argues that Dr. Bray's letters "are not medical records." Resp't's Posthr'g Br. at 30. Due to the importance of Dr. Bray and his records, his background and the origin of his records are described in some detail.

Preliminarily, information about Dr. Bray comes from various sources. In July 2003, Mr. D'Angiolini filed records from Dr. Bray as exhibit 17. Although the earliest record authored by Dr. Bray contained in exhibit 17 is a letter dated November 30, 1999, see exhibit 17 at 15; Tr. 313, Mr. D'Angiolini saw Dr. Bray before November 30, 1999. Mr. D'Angiolini did not file those earlier records before the fact hearing held on August 8, 2007. See Tr. 309-10.

On December 3, 2007, Mr. D'Angiolini filed records his former attorney had obtained from Dr. Bray's office, covering treatment from July 1997 to February 1998. In total, there were four appointments and Dr. Bray's typed notes appear on 16 lines. Exhibit 61.

On April 16, 2008, Mr. D'Angiolini, again acting through his former attorney, filed three letters from Dr. Bray. The dates of the letters are November 6, 1997, November 13, 1997, and January 22, 1998. Each letter is typed and signed. Two letters are one paragraph and one letter is two paragraphs. Exhibit 73.

On December 19, 2011, Mr. D'Angiolini's current attorney filed a four-page letter that Dr. Bray wrote to an insurance company on May 9, 2002. In this letter, Dr. Bray summarized not only the care that Dr. Bray had provided but also information provided by other doctors. Dr. Bray stated that he last treated Mr. D'Angiolini on May 9, 2002, the date of the letter, although no notes of treatment were provided. Exhibit 131.

Other information about Dr. Bray comes from testimony given in either the workers' compensation proceeding or this claim. In both settings, Mr. D'Angiolini and his mother testified about Dr. Bray's treatment of Mr. D'Angiolini. Although Dr. Bray testified as part of the case for workers' compensation benefits, the scope of the testimony was intended to be limited to when Mr. D'Angiolini learned that the hepatitis B vaccine harmed him. See exhibit 50 at pdf 205 (Bray Dep. Tr. 5). These disparate sources of information combine to show the following facts about Dr. Bray's treatment of Mr. D'Angiolini.¹⁵

Dr. Bray graduated medical school in 1948 and became licensed to practice medicine in Pennsylvania in 1950. He was a general practitioner, not board certified in any field, and did not hold himself out as a specialist in any field of medicine. Exhibit 50 at pdf 206 (Bray Dep. Tr. 6). Ms. D'Angiolini described Dr. Bray as "a country doctor. . . . [I]f you had a cold, you didn't make an appointment with him. You just went in and he would see you. . . . First come, first serve." Tr. 491. Mr. D'Angiolini, too, stated that Dr. Bray was "a country guy." Tr. 313; accord exhibit 51 at pdf 45 (June 7, 2001 W.C. Trial Tr. 33).

Mr. D'Angiolini began seeing Dr. Bray in 1987 or 1988. Tr. 313. However, there are no documents reflecting any appointments. Dr. Bray stated that his first appointment with Mr. D'Angiolini was on February 5, 1996, although there are also no documents reflecting this appointment. Exhibit 50 at pdf 208 (Bray Dep. Tr. 8).

The first appointment for which there is a record occurred on July 29, 1997,¹⁶ between the dates on which Mr. D'Angiolini received the second and third

¹⁵ In some of the quotations from Dr. Bray's records, the capitalization has been changed without notation.

¹⁶ Mr. D'Angiolini did not recall when he had most recently seen Dr. Bray before the July 29, 1997 visit. Tr. 615-16.

doses of the hepatitis B vaccine. See Findings of Fact at 27. At this appointment, Mr. D'Angiolini was complaining of "nasal stuffiness" and "AM bloody / yellow discharge." Dr. Bray's impression was sinus infection and he prescribed erythromycin. There is no indication of fatigue or tiredness. Exhibit 61.

The next appointment was on November 6, 1997, which was the day after Mr. D'Angiolini stopped working. His mother brought him to see Dr. Bray. Tr. 433, 492. Dr. Bray's typed notes indicate that Mr. D'Angiolini was complaining of "extreme fear, feel[ing] immobilized, afraid to leave the house, not caring for himself or his environment." Exhibit 61. Ms. D'Angiolini testified that Dr. Bray did not perform a physical examination, Tr. 493, and Dr. Bray's notes appear in accord with this recollection. Dr. Bray's impression was "severe depression / adjustment disorder / panic disorder / agoraphobia" and he prescribed amitriptyline and Valium. Exhibit 61.

Dr. Bray wrote a letter addressed "To Whom It May Concern" on November 6, 1997. Dr. Bray stated that Mr. D'Angiolini was under his care for "major depression" and Dr. Bray stated that Mr. D'Angiolini could not work. Exhibit 73 at 3.

A follow up appointment was held seven days later on November 13, 1997. The office notes are two typed lines, indicating that Mr. D'Angiolini had not improved and that Dr. Bray was increasing the dose of amitriptyline. Exhibit 61. The letter associated with this visit is similar. It states that Mr. D'Angiolini is being treated for "major depression" and "panic disorder" and cannot work. Exhibit 73 at 1. Dr. Bray signed Mr. D'Angiolini's application for disability benefits on December 15, 1997. Exhibit 16 at 145-46. In Mr. D'Angiolini's application for disability benefits, Dr. Bray described his symptoms as "crying, unable to stay awake, not caring for self, shortness of breath, dizziness, heart races, chest pain, extreme fear, feel immobilized, afraid to go out."

Dr. Bray's next activity was writing a letter in support of Mr. D'Angiolini's claim for disability benefits on January 22, 1998. There are no office notes associated with this visit and the letter essentially repeats the information in the November 6, 1997 and November 13, 1997 letters. Exhibit 73 at 2; cf. exhibit 16 at 97 (letter from insurance company to Mr. D'Angiolini in response to Dr. Bray's letter).

The last office notes from Dr. Bray are dated February 12, 1998. Dr. Bray recorded that Mr. D'Angiolini was complaining of "severe anxiety and increased

symptoms.” Dr. Bray prescribed BuSpar and continued other medications. Exhibit 61.

2. Treatment with Other Doctors in 1998

Mr. D’Angiolini continued to see Dr. Middleman and Ms. Casella, the psychologist who was counseling him. They diagnosed him as suffering from OCD, anxiety, and depression. Exhibit 24 at 15, 17; exhibit 61 at 1; Tr. 45-49.

In April 1998, Mr. D’Angiolini reported that he was “quite active” and running. Exhibit 15 at 12; but see Tr. 505-06, 630. On April 12, 1998, Mr. D’Angiolini went to Leigh Valley Hospital because of a headache and chest pain. Mr. D’Angiolini described the chest pain as “mild” and his headaches as “typical for his migraines other than being a bit longer lasting.” Exhibit 15 at 12.

By the end of April 1998, Mr. D’Angiolini was not taking care of his apartment and the local Board of Health became involved. Mr. D’Angiolini’s mother cleaned his apartment and moved her son to her house. Tr. 255-56, 437-38; exhibit 51 at pdf 198 (May 31, 2002 W.C. Trial Tr. 60); exhibit 54 ¶ 32-34 (Ms. D’Angiolini’s affidavit describing her observations of Mr. D’Angiolini when he was living with her); exhibit 51 at pdf 39 (June 7, 2001 W.C. Trial Tr. 27) (Mr. D’Angiolini’s testimony).

In June, July and August 1998, Mr. D’Angiolini saw Ms. Casella. She believed that he could not work. For the July 1998 form to certify Mr. D’Angiolini’s entitlement to disability benefits, Ms. Casella wrote that Mr. D’Angiolini “continues to struggle regularly with sleeping difficulties. He finds that living with parents causes other stress in his life because of sometime volatile relationship with father. Panic attacks continue and he’s having difficulty getting himself on a functional schedule.” Exhibit 16 at 111. Her diagnoses were “adjustment disorder with depressed mood” and “panic disorder with agoraphobia severe.” Id.

On October 10, 1998, Mr. D’Angiolini saw Dr. Gregory Bach, whose letterhead states that he is board certified in family medicine and addiction medicine. Exhibit 5 at 21.¹⁷ Dr. Bach’s handwritten notes, which are difficult to

¹⁷ Dr. Shoenfeld stated that Dr. Bach is a specialist in infectious diseases. Tr. 854-55.

decipher, indicate that Mr. D'Angiolini's chief complaints included "sweats, [weight] gain, stomach problems, heart palpitations, twitching headache, neck stiffness, light sensitivity, light head, confusion, difficulty with speech, mood swings, depression." Dr. Bach's impressions included: "1. Fibromyalgia, 2. Chronic fatig. 3. Myopathy." Id. at 26. This October 10, 1998 reference to chronic fatigue appears to be the earliest reference to this symptom in Mr. D'Angiolini's medical records by a medical doctor. See Tr. 1281. Dr. Bach ordered an echocardiogram and also blood work. Exhibit 5 at 26; see also Tr. 440-41, 684.

In most respects, the blood work was normal, including a showing that Mr. D'Angiolini did not have antinuclear antibodies. Exhibit 5 at 12-13; exhibit 23 at 87-92. The echocardiogram was basically normal, although it did reveal mild hypokinesia. Exhibit 23 at 115. "Hypokinesia" means abnormally decreased mobility, motor function, or activity. Dorland's Illustrated Medical Dictionary 903 (32nd ed. 2012) ("Dorland's").

On November 10, 1998, Mr. D'Angiolini had an appointment with Dr. Roman for the first time after he received the hepatitis B vaccination. He complained about headaches, nausea, depression / anxiety, and fatigue. Exhibit 23 at 32; see also exhibit 50 at pdf 151, 268 (Genovese Dep. Tr. 62; Roman Dep. Tr. 29). Tests that she ordered indicated that Mr. D'Angiolini was infected with or had been infected with the Epstein-Barr virus. Exhibit 50 at pdf 263, 267 (Roman Dep. Tr. 24, 28). Dr. Roman was concerned about how Mr. D'Angiolini's heart was functioning. Therefore, she referred him to additional doctors for testing. See exhibit 23 at 114; exhibit 50 at pdf 312 (Roman Dep. Tr. 73).

Mr. D'Angiolini told a cardiologist (Dr. Weber) that he was having "dyspnea on exertion when he is doing a strenuous exercise such as heavy lifting or walking while carrying a heavy parcel" for one year. Exhibit 6 at 17 (record dated Nov. 13, 1998). Mr. D'Angiolini's heart was tested in SPECT cardiac perfusion scan on November 20, 1998. The result showed a "mild decrement in LVEF, 44% with questionable borderline inferior wall ischemia." Exhibit 17 at 5. Mr. D'Angiolini was diagnosed as having cardiomyopathy. Exhibit 5 at 6 (report of Dr. Frederic J. Weber); see also Tr. 510.

Mr. D'Angiolini went to the Penn Center for Healing, where Dr. Anne Norris saw him. His chief complaint was "fatigue." The history Dr. Norris obtained recounts that Mr. D'Angiolini had "sudden onset fatigue" in late June

1997. Her record indicates that Mr. D'Angiolini has "been out of work for a year [secondary to] fatigue."¹⁸ Dr. Norris created a series of notes, corresponding to the ancillary symptoms associated with CFS. For example, she stated that Mr. D'Angiolini did not get refreshing sleep, did get headaches, but did not have either joint symptoms or muscle pain. Dr. Norris's impression was "not CFS by criteria." Exhibit 22 at 4 (Nov. 17, 1998).

By December 1998, Dr. Middleman had lost touch with Mr. D'Angiolini. She was sufficiently concerned about him that she called Ms. Casella. Exhibit 24 at 19; Tr. 54-55.

3. Return to Dr. Bray and Treatment with Dr. Buttram and Dr. Waisbren in 1999

After the visit with Dr. Norris in November 1998, Mr. D'Angiolini had one follow-up appointment with her. Exhibit 22 at 2 (Jan. 19, 1999). Following this appointment, there appears to be a gap in visits with doctors. Resumed medical attention began in August 1999.

According to a letter Dr. Bray wrote on June 20, 2002, "[o]n August 3, 1999, while on the internet, I came across information about a fund for people injured by the hepatitis B vaccination. . . . The patient's mother, Cynthia D'Angiolini, came to my office on August 5, 1999[,] and I gave her the information and the name of a Doctor who might be able to help Joseph." Exhibit 16 at 229.¹⁹ Mr. D'Angiolini

¹⁸ This history is not entirely consistent with the Findings of Fact.

¹⁹ This letter does not appear in any of the files Mr. D'Angiolini obtained directly from Dr. Bray. Rather, the source of this information is Mr. D'Angiolini's employment records from Valley Forge Medical Center. In the course of the workers' compensation proceeding, Mr. D'Angiolini's employer challenged the accuracy of the account in which Dr. Bray told Ms. D'Angiolini about the Vaccine Program. See exhibit 16 at 336 (post-hearing brief). This assertion was the basis of the employer's argument that Mr. D'Angiolini's claim for workers' compensation benefits was untimely. On the other hand, Mr. D'Angiolini testified that Dr. Bray first suggested that there was a causal connection between the hepatitis B vaccine and his condition. Exhibit 51 at pdf 120 (August 3, 2001 W.C. Trial Tr. 60).

identified this doctor as Burton Waisbren. Exhibit 51 at pdf 52, 54 (June 7, 2001 W.C. Trial Tr. 40, 42).²⁰

It is worthwhile to interrupt the recitation of Mr. D'Angiolini's medical history with a brief discussion of his legal claims. On August 4, 1999, Mr. D'Angiolini, acting through Attorney Clifford Shoemaker, filed the pending case in the Court of Federal Claims. Also, on November 29, 1999, Mr. D'Angiolini's mother sent a letter notifying Valley Forge Medical Center that the hepatitis B vaccinations harmed her son. Exhibit 16 at 68; see also exhibit 51 at pdf 210-11 (May 31, 2002 W.C. Trial Tr. 72-73). Hence, from early August 1999, Mr. D'Angiolini was alleging that the hepatitis B vaccinations injured him.

On October 6, 1999, Mr. D'Angiolini saw Dr. Harold Buttram, whose office is in Quakertown, Pennsylvania, which is relatively near Mr. D'Angiolini's home. Exhibit 17 at 125. Dr. Buttram ordered a series of laboratory tests. Id. at 126-30. After the results of these tests were reported to Dr. Buttram, he saw Mr. D'Angiolini again on November 1, 1999. Dr. Buttram wrote a handwritten letter, stating in its entirety:

Joseph D'Angiolini was seen by me Oct 6th and again today [November 1, 1999]. He is now disabled with chronic fatigue and myocarditis.

He was in excellent health until he had a series of hepatitis B immunizations March, April, [and] October 1997.

He was badly crippled after 2nd injection, virtually bed fast [sic] after the third. All of heart-related symptoms date back to that time.

A causal relation of the hepatitis [vaccine] with his present myocarditis is highly probable.

Exhibit 17 at 125. Dr. Buttram's letter appears in Dr. Bray's file, although nothing in Dr. Buttram's letter indicates that Dr. Buttram mailed the letter to Dr. Bray.²¹

²⁰ Dr. Bray stated that he did not refer Mr. D'Angiolini to Dr. Waisbren. Exhibit 50 at pdf 229-30 (Dr. Bray Tr. at 29-30). If Dr. Bray did not refer Mr. D'Angiolini to Dr. Waisbren, then it is likely that Dr. Bray referred Mr. D'Angiolini to Harold Buttram. The only doctors whom Mr. D'Angiolini saw at the end of 1999 were Dr. Buttram and Dr. Waisbren.

On November 30, 1999, Dr. Bray wrote another letter to the disability insurance company in support of Mr. D'Angiolini's claim for benefits. This letter is noticeably longer than Dr. Bray's previous letters. One possible explanation is that Mr. D'Angiolini or Mr. D'Angiolini's mother provided Dr. Bray with letters from Doctors Weber (a cardiologist), Bach (a specialist in family medicine and addiction counseling), and Black (a gastroenterologist). In any event, a portion of Dr. Bray's letter states:

Joseph M. D'Angiolini is a patient under my care. He was originally put out [sic] on disability for depression. He had come to my office on November 6, 1997, after seeing a psychologist who felt he was depressed due to argument with his father. He complained of chest pain, shortness of breath, palpitations, feeling like he would pass out, sweating, color changes, and extreme fatigue, aches and pains, etc. . . . He has a history of allergies (penicillin, sulfa, yeast, cigarette smoke, seasonal allergies) and sinus problems.

He returned to my office for medications but had no improvement in his condition. After treating him for quite a length of time the psychologist informed him that she felt his problem was [a] medical problem and recommended he get a full medical workup. The physical workup revealed that he has cardiomyopathy; global hypokinesia of the left ventricle, and decreased LVEF, questionable inferior wall ischemia. In addition he has Chronic Fatigue Syndrome; depression is secondary to his physical condition and the limitations and changes in his lifestyle due to his health.

* * *

He is 100% completely and totally disabled due to chronic fatigue and pain. He is not able to work in any capacity. He will be reevaluated in 6 months.

²¹ Additional details about Dr. Buttram's treatment of Mr. D'Angiolini appear in exhibit 36.

Exhibit 17 at 15. At his deposition, Dr. Bray explained that the diagnoses of cardiomyopathy, etc. as well as the diagnoses of chronic fatigue syndrome and depression came from another doctor. Exhibit 50 at pdf 228 (Bray Dep. Tr. 28).

On December 9, 1999, Mr. D'Angiolini saw Dr. Burton A. Waisbren, whose office is located in Milwaukee, Wisconsin.²² See exhibit 20 at 10, 21 (intake form dated December 9, 1999). Mr. D'Angiolini's mother brought him to the appointment. Tr. 443. Dr. Waisbren stated, in his deposition, that people from all over the country come to see him because he had stated that hepatitis B vaccine can cause autoimmune diseases and information about his opinions was available on the internet. Exhibit 50 at pdf 13-17 (Waisbren Dep. Tr. 9-13).

Dr. Waisbren is board certified in internal medicine. He described himself as having "particular expertise in immunology and infectious diseases and critical care." Exhibit 50 at pdf 8 (Waisbren Dep. Tr. 4). He stated that there is not a certifying body for immunology. He also stated that although there is a certifying body for infectious diseases, he did not attempt to obtain board certification because he had already been teaching infectious disease and immunology for at least 15 years. Exhibit 50 at pdf 17-18 (Waisbren Dep. Tr. at 13-14).

During the December 9, 1999 appointment, Dr. Waisbren obtained information about Mr. D'Angiolini's history, conducted a physical examination, and ordered multiple laboratories studies. He wrote a lengthy case report about Mr. D'Angiolini, which he sent to Dr. Bray. Exhibit 17 at 37-43.²³ For Mr. D'Angiolini's history, Dr. Waisbren recounted:

²² In a document dated December 8, 1999, which is one day before Dr. Waisbren saw Mr. D'Angiolini, Dr. Waisbren offered a "presumptive diagnosis." Dr. Waisbren stated "Post vaccinal encephalomyelitis and acquired auto immunity involving in addition to the central nervous system the heart and muscles. Theoretically this is due to a combination of antigens one of which exhibits molecular mimicry." Exhibit 21 at 39.

²³ Dr. Waisbren also wrote to Professor Peter H. Meyers, an attorney, who supervises a clinic at George Washington University Law School, asking Professor Meyers to assist Mr. D'Angiolini with his claim in the Vaccine Program. Exhibit 17 at 36. This referral was unnecessary because Mr. Shoemaker already represented Mr. D'Angiolini in the Vaccine Program.

After the first hepatitis B injection he experienced malaise and muscle and joint aches and headaches.

After a second injection in April, 1997, he noted severe headaches and had several episodes of blacking out. He also developed severe fatigue.

He was given a third injection after which he became completely unable to function and went into a fugue that lasted a year. He remembers little of it other than he lay disheveled in his unke[m]pt apartment and was unable to perform daily hygiene and food preparation. After this time, a psychiatrist who had been treating him for depression decided that there was an organic cause for his problem. He then moved in with his devoted parents who gave him general support.

In mid-1998 he was seen by a variety of doctors, none of whom could make a definitive diagnosis regarding his extreme fatigue, muscle pains, and impaired cognitive ability.

Exhibit 17 at 37. Dr. Waisbren's conclusion was:

This young man is suffering from post vaccinal encephalomyelitis and generalized autoimmunity due to the hepatitis B vaccine. At this point, he is completely disabled.

The syndrome of post vaccinal encephalomyelitis is well-established in the medical literature. Vann Roogens standard test in virus disease listed hundred[] of reports in the medical literature in its regard. The enclosed two case reports report two similar cases due to hepatitis B vaccination.

Id. at 39. Dr. Waisbren also proposed a "hypothetical analysis." He stated:

The multiple autoimmunity syndrome we witness here is the result of multiple immune challenges that fit into the syndrome of Root-Bernstein who has noted it to occur in AIDS patients. Four criteria for this syndrome are 1.) molecular mimicry between an antigen and human tissue, 2.) compl[e]mentarity between a second antigen and the first one, 3.) the presence of an immune adjuvant that could have been supplied in this case by a bacterial infection (muramyl peptide) or the

aluminum in the vaccine, and 4.) an HLA pattern that precedes autoimmunity.

Id. at 41. It appears that Dr. Waisbren sent several articles that called into question the safety of hepatitis B vaccine to Dr. Bray. Authors of those articles included Bonnie Dunbar, Barbara Loe Fisher, and Dr. Waisbren. See exhibit 17, *passim*. In his deposition, Dr. Bray characterized Dr. Waisbren as a “super specialist.” Exhibit 50 at pdf 232 (Bray Dep. Tr. 32).

4. Correspondence from Dr. Bray in 2000 and 2002

It appears that Dr. Bray saw Mr. D’Angiolini again in February 2000. Exhibit 17 at 159 (tests for blood collected on February 2, 2000).²⁴ On February 22, 2000, Dr. Bray wrote another letter to the insurance company. (This letter is one on which Mr. D’Angiolini heavily relies.)

He had extreme fatigue, chest pain, palpitations, [shortness of breath] with exertion, nausea, diaphoresis, aches and pains, and etc., mid to late June of 1997. His symptoms continued to increase; all he was able to do was sleep and drag himself to work. Due to his extreme fatigue he was not able to care for himself or his environment. He felt like something was wrong with his brain in that he wasn't able to concentrate and was having memory/thinking problems. . . .

Approximately October 26, 1997, his condition became worse. He felt "dead", all his symptoms increased; he was sleeping all the time, felt as though his heart was pounding through his chest, had extreme chest pain, shortness of breath, diaphoresis, felt as though he would pass out, his joints and muscles ached, and etc. He felt anxious, panicky and depressed due to his health. Because he was sleeping[] excessively, feeling depressed and panicky, and had an altercation with his father in September 1997, it was assumed that he was suffering from Depression and Panic Disorder. HOWEVER, onset of the illness and symptoms preceded the altercation by several months.

²⁴ There are no office notes from Dr. Bray for a visit in February 2000.

Id. at 109-10. Dr. Bray's letter also identified the following diagnoses as present in Mr. D'Angiolini: "Systemic Autoimmune Disease, Cardiomyopathy, Post Encephalomyelitis, Depression secondary to chronic illness and limitations/changes in lifestyle due to illness."²⁵ Dr. Bray then listed more than 20 "subjective symptoms" and more than 20 "objective clinical findings" and commented that "[t]he onset of the illness was mid to late June of 1997." Id. Dr. Bray repeated much of this information in another letter concerning Mr. D'Angiolini's disability insurance benefits after Dr. Bray saw Mr. D'Angiolini on September 16, 2000. Exhibit 16 at 247.

Dr. Bray wrote a final letter to the insurance company on May 9, 2002, which was a day that Dr. Bray saw Mr. D'Angiolini. Exhibit 131. The background information about Mr. D'Angiolini's health in 1997 is the same as the history in the February 22, 2000 letter. Dr. Bray, for the first time, summarizes visits with Doctors Bach, Norris, Weber, Black, Day, Buttram, Waisbren, Bellanti, Mandel, and Vasey. However, there is no indication that Dr. Bray was aware of Mr. D'Angiolini's treatment with Dr. Middleman.

Dr. Bray stated that Mr. D'Angiolini "clearly meets the 1982 revised criteria for classification of Systemic Lupus Erythematosus, of the American College of Rheumatology (See attached copy; the patient's objective findings found on physical examination in my office or on lab studies are highlighted for your convenience), involving multiple body systems; central nervous system/neurological, cardiovascular, joint, muscle, renal and mental." Other diagnoses are repeated from the February 22, 2000 letter, including "cardiomyopathy, post encephalomyelitis, neuropathy, [and] depression." Id. Dr. Bray listed numerous subjective symptoms, many more than were listed previously. Dr. Bray also repeated the objective clinical findings and added results of a physical examination. Id. at 6.

²⁵ Dr. Waisbren used the term "post vaccinal encephalomyelitis." Exhibit 17 at 39. However, Dr. Bray's reports consistently say "post encephalomyelitis." Whether Dr. Bray intended to drop the word "vaccinal" is not clear.

5. Visits with Doctors Other than Dr. Bray in 2000 through 2003²⁶

As Dr. Bray mentioned in his May 9, 2002 letter, Mr. D'Angiolini saw other doctors, including Dr. Bellanti, Dr. Mandel, and Dr. Vasey.

The appointment with Dr. Joseph Bellanti was on March 2, 2000. Exhibit 3 at 1. Dr. Bellanti's letter was written to Mr. D'Angiolini's attorney, Mr. Shoemaker, *id.*, and Mr. D'Angiolini saw Dr. Bellanti at Mr. Shoemaker's request. Tr. 635. On the questionnaire for Dr. Bellanti, Mr. D'Angiolini stated that he is allergic to yeast, exhibit 3 at 4, and Dr. Bellanti recounted this allergy in the letter to Mr. Shoemaker, *id.* at 1-2. Dr. Bellanti's letter also stated that "[w]ithin 24 hours of receiving the [first dose of the hepatitis B] vaccine he developed symptoms of malaise, muscle and joint pains, headaches and an overall 'flu like' syndrome." Exhibit 3 at 1. Dr. Bellanti concluded his letter by stating, "I strongly suspect that there is a causal relationship between the hepatitis B vaccination which he received and the symptoms which he is undergoing." *Id.* at 2.

A few days after seeing Dr. Bellanti, Mr. D'Angiolini passed out while walking and fractured his thumb. Exhibit 13 at 8-9. He had an operation to repair the fracture. Exhibit 14 at 60-62. During the convalescence for his thumb fracture, Mr. D'Angiolini saw Dr. Scott M. Fried. Dr. Fried stated that Mr. D'Angiolini was "back playing the guitar for a number of hours at a time and also the piano. He is really not limited in any activities." Exhibit 19 at 3. Mr. D'Angiolini, in the hearing, denied that he was playing the guitar or the piano. *See* Tr. 635-38.

On July 28, 2000, Mr. D'Angiolini had an appointment with Dr. Buttram. Dr. Buttram's history states that Dr. Waisbren from Wisconsin saw Mr. D'Angiolini in December 1999, and Dr. Waisbren diagnosed Mr. D'Angiolini with "post vaccinal encephalitis and generalized autoimmunity." Dr. Buttram's impression was "post vaccinal encephalitis and severe fatigue." Exhibit 36 at 3-4.

²⁶ Since the events after 2000 occurred more than three years after Mr. D'Angiolini's most recent hepatitis B vaccination, this recent history is presented more summarily. For example, Mr. D'Angiolini saw Dr. Roman periodically. Exhibit 23 at 8-28; exhibit 50 at pdf 276-77 (Roman Dep. Tr. 37-38). The details of these visits with Dr. Roman do not affect the outcome of Mr. D'Angiolini's claim for compensation. Thus, this decision discusses only the most relevant medical records.

On September 29, 2000, Mr. D'Angiolini saw Frank Vasey, a rheumatologist at the University of South Florida College of Medicine. Exhibit 133 at 18. Dr. Vasey, as discussed below, wrote reports stating that the hepatitis B vaccine harmed Mr. D'Angiolini and testified to that harm at the hearing. See sections IV.A, V.A.1, and VII.A.1 below. During the September 29, 2000 appointment, Mr. D'Angiolini provided a history to Dr. Vasey.

Mr. D'Angiolini's account, as written by Dr. Vasey, begins:

he had been in good health until 03/97, at which point he was advised by his employer to have the hepatitis B vaccine. After the first injection he developed promptly some headaches and flu-like symptoms. These problems persisted over several weeks, and he received another vaccination in 04/97, "I was out of it." He was dragging himself to work.

Id. In connection with the third dose of the vaccination, Dr. Vasey's understanding was: Mr. D'Angiolini "had another reaction with chest pain, shortness of breath, sweats and worsening of his flu-like symptoms. By 11/97, he had been granted a short-term disability. . . . He saw a psychiatrist, who eventually concluded that he had an organic problem." Id.

In terms of Mr. D'Angiolini's current problems, Mr. D'Angiolini told Dr. Vasey that he had "chronic fatigue, muscle and joint pain." Id. Dr. Vasey conducted a physical examination, too. Dr. Vasey's impression was that Mr. D'Angiolini "has an immune reaction to hepatitis B vaccination. This is complicated by chronic fatigue and fibromyalgia." Dr. Vasey recommended that Mr. D'Angiolini limit his activity level. Id. at 18-19.

Following Dr. Vasey's examination of Mr. D'Angiolini, Dr. Vasey wrote a letter to the judge presiding over Mr. D'Angiolini's claim for workers' compensation benefits pending in Pennsylvania. Dr. Vasey stated "On reviewing his clinical course I believe he suffered an unusual immune mediated reaction to his Hepatitis B vaccine." Dr. Vasey continued: "Because the recognition of this problem is at the case report level[,] well intention[ed] honest physicians could contest my opinion." Dr. Vasey recommended that the judge postpone the hearing scheduled in the workers' compensation claim to accommodate Mr. D'Angiolini's illness and "to allow better understanding of the immunology and epidemiology of the vaccine reactions." Exhibit 133 at 23.

In March 2001, Mr. D'Angiolini again saw Dr. Buttram, whose history noted Mr. D'Angiolini's pending claims for disability benefits and workers' compensation benefits. Dr. Buttram's impressions were hepatitis B and influenza vaccine reactions, myocarditis, encephalomyelitis, neuropathy, chronic fatigue, fibromyalgia, and temporal arteritis. Exhibit 36 at 1-2. Another appointment with Dr. Buttram was on August 7, 2001. Exhibit 14 at 8-10.

In July 2001, Mr. D'Angiolini returned to Dr. Waisbren, whom he had previously seen in 1999. Proceedings in Mr. D'Angiolini's workers' compensation claim may have prompted these appointments as Dr. Waisbren directed his report to Mr. D'Angiolini's attorney.²⁷ Dr. Waisbren confirmed his 1999 opinion that the hepatitis B vaccine had harmed Mr. D'Angiolini. Dr. Waisbren indicated that Mr. D'Angiolini had "some unsteadiness on his feet, some hesitance of speech, and a markedly positive fibromyalgia test." Exhibit 16 at 241-42.²⁸

On September 19, 2001, Mr. D'Angiolini had his second appointment with Dr. Vasey. Exhibit 133 at 17. The third appointment was on July 30, 2003. *Id.* at 16.

On June 3, 2003, Mr. D'Angiolini saw Harold Pretorius, M.D., whose office is in Cincinnati, Ohio. Dr. Pretorius's file includes records from a 1998 test on Mr. D'Angiolini's heart, the May 1999 echocardiogram, and reports from Dr. Weber. Exhibit 40 at 4-11. Dr. Pretorius noted that Mr. D'Angiolini's physician was "Frank Vasi" [sic]. *Id.* at 2. Dr. Pretorius's history indicated, among other things, that Mr. D'Angiolini had "[s]yncope causing several automobile accidents and a fall with fracture of the left thumb, myalgia, chronic fatigue and somnolence, . . . severe headaches recently requiring daily analgesics." Dr. Pretorius also stated that Mr. D'Angiolini's lab tests showed "low C3 complement, positive double-stranded DNA, antimitochondrial, anti-smooth muscles and antimyocardial antibodies." *Id.*²⁹

²⁷ The judge in the workers' compensation case first received testimony in Mr. D'Angiolini's case on June 7, 2001. Exhibit 51 at pdf 13-15 (June 7, 2011 W.C. Trial Tr. 1-3).

²⁸ The fibromyalgia test appears as exhibit 21 at 51.

²⁹ None of the lab tests produced with Dr. Pretorius's file show low C3 complement, etc. On the other hand, the 1998 heart study, which is included in Dr. Pretorius's file, indicated that Mr. D'Angiolini had global hypokinesia.

Dr. Pretorius administered a SPECT scan of Mr. D'Angiolini's brain.³⁰ Dr. Pretorius noted three results. There was a "[n]ormal posterior dynamic flow study tracer distribution" and a "[n]ormal stimulated cerebral perfusion." However, there was also a "[d]ecreased baseline (FDG) right parieto-occipital, left temporal and cerebellar tracer distribution." Dr. Pretorius stated that this abnormal finding was "consistent with nonspecific neurodegeneration." *Id.* at 3. After ruling out several conditions such as multiple sclerosis, Dr. Pretorius suggested that the results may be consistent with "[l]upus-like cerebritis (evidenced also by positive double-stranded DNA antibodies) related to repeated antigen (vaccine) exposure . . . most likely in a patient with multiple documented allergies." *Id.* at 2. What Dr. Pretorius did with these results is not readily apparent.³¹

6. Cleveland Clinic Doctors, including Doctors Hanson and Galatro, in 2004 and 2005

On June 30, 2004, Mr. D'Angiolini had an appointment with an office of the Cleveland Clinic located in Naples, Florida. An advanced registered nurse practitioner and Maurice Hanson, a neurologist, saw him at this visit, which appears to have been Mr. D'Angiolini's first visit to the Cleveland Clinic. Exhibit 37 at 22, 29. Dr. Hanson's notes indicate that Mr. D'Angiolini brought with him medical records from other doctors, including Doctors Bray and Bach. Dr. Hanson also recounted that Dr. Bellanti "thought that he had an autoimmune disease related to vaccinations with hepatitis B." *Id.* at 24. At this point, Dr. Hanson's impression was "there is some conflicting data and many interpretations, all of which need to be further elucidated," and Dr. Hanson referred Mr. D'Angiolini for additional consultations. *Id.*

One of these consultations was for a neuropsychological examination, which according to Dr. Hanson, took place in Philadelphia. Following that consultation, Mr. D'Angiolini saw Dr. Hanson again on September 23, 2004. Dr. Hanson

³⁰ SPECT is an acronym standing for single-photo emission computed tomography. *Dorland's* at 1742.

³¹ Dr. Pretorius's report appears not to be included in any treating doctor's records. Nevertheless, the expert witnesses discussed Dr. Pretorius's SPECT scan in their reports. *See* exhibit 97 at 2 (Dr. Shoenfeld); exhibit A at 7-8 (Dr. Lightfoot); exhibit 153 at 1 (Dr. Buttram).

determined that the notes from the neuropsychological examination “did not document any evidence of psychosis or a psychiatric disorder.” Id. at 25.

Dr. Hanson referred Mr. D’Angiolini to a specialist in infectious disease, Margaret J. Gorenssek. Dr. Gorenssek’s history is again relatively lengthy, drawing upon reports of different doctors. She stated “the patient had so many evaluations, so many differing opinions, that there is no one consistent opinion which makes it more suspicious that there really is not any significant opinion.” Exhibit 37 at 21. It appears that Dr. Gorenssek ordered a series of laboratory tests. Id. at 26; see also id. at 1-17 (results).

On October 19, 2004, Mr. D’Angiolini had an appointment with Dr. Hanson on an “emergent basis” because of severe headaches. In this record, Dr. Hanson stated that Mr. D’Angiolini had been diagnosed with cardiomyopathy. Dr. Hanson referred Mr. D’Angiolini to Dr. Galatro, a cardiologist. Dr. Hanson’s examination of Mr. D’Angiolini on October 19, 2004, was “essentially normal.” Id. at 26-27. An echocardiogram and more laboratory tests were done. Id. at 1-19.

On November 19, 2004, Mr. D’Angiolini returned to the Cleveland Clinic and saw Dr. Hanson. Dr. Hanson noted that he (Dr. Hanson) had consulted Dr. Galatro. Whether Dr. Galatro actually saw Mr. D’Angiolini on this date is less clear because her notes do not contain any details. Exhibit 37 at 19. Dr. Hanson, however, recounted that “I rather agree with Dr. Galatro that this is an autoimmune disorder which falls presum[ably] into the lupus category.” Id. at 25. Dr. Hanson again referred Mr. D’Angiolini to more doctors, but records of a consultation with Dr. Goodwin and an ear, nose, and throat specialist do not appear in the record. Dr. Hanson concluded “I will see him back a later date.” Id.

A note evidencing a further appointment with Dr. Hanson does not appear in the record. However, Mr. D’Angiolini saw Dr. Galatro on June 22, 2005, which was his most recent visit to the Cleveland Clinic. Dr. Galatro recorded, as part of Mr. D’Angiolini’s history, that he “has chronic fatigue syndrome, SLE, and cardiomyopathy.” Her assessment includes “[m]ild cardiomyopathy” and “SLE,” but not chronic fatigue syndrome. Dr. Galatro prescribed medication for his cardiomyopathy but did not recommend any particular treatment or study specifically for SLE. Id. at 20.

7. Recent Visits with Dr. Vasey

When Mr. D’Angiolini testified in April 2008, he stated that he was not functioning very well. Tr. 688. He stated that he had neurological problems and

“horrible” physical pain. Tr. 690. When asked about his current doctors, Mr. D’Angiolini stated that he saw Dr. Vasey about twice a year. Tr. 693.

Dr. Vasey’s records confirm that he saw Mr. D’Angiolini about twice a year from 2003 to 2009. Exhibit 133 at 1-15. By the time of the hearing in January 2013, Mr. D’Angiolini’s most recent appointment with Dr. Vasey was on June 6, 2012. Tr. 1525; exhibit 196.

IV. General Assessment of Witnesses

The Federal Circuit has made clear that special masters have the responsibility “to assess the reliability of testimony, including expert testimony.” Moberly v. Sec’y of Health & Human Servs., 592 F.3d 1315, 1325 (Fed. Cir. 2010). The Federal Circuit expects that special masters will “make determinations as to the reliability of the evidence presented to them and, if appropriate, as to the credibility of the person presenting that evidence.” Id. at 1326.

These instructions are the basis for a general evaluation of the witnesses who testified at the January 2013 hearing: Doctors Vasey, Shoenfeld, Lightfoot and Whitton.

A. Dr. Vasey

Among the people who testified, Dr. Vasey stands in a unique position. He actually treated Mr. D’Angiolini. Mr. D’Angiolini first came to Dr. Vasey in 2000, which is approximately three years after the vaccinations at issue. Since 2000, Dr. Vasey has periodically examined, ordered various tests for, and recommended treatment for Mr. D’Angiolini. See exhibit 133.

As a treating doctor, Dr. Vasey’s opinion warrants very careful consideration. Capizzano v. Sec’y of Health & Human Servs., 440 F.3d 1317, 1326 (Fed. Cir. 2006). Here, Dr. Vasey’s diagnoses are worth a great deal. No one has criticized the care that he provided to his patient. No one has suggested that Dr. Vasey should have ordered more tests and no one has suggested that Dr. Vasey misinterpreted the results of the tests he ordered. In short, there is every reason to defer to Dr. Vasey’s assessment of the disease that afflicts Mr. D’Angiolini. As discussed below Dr. Vasey’s opinion that Mr. D’Angiolini does not suffer from SLE is almost definitive evidence on that point.

However, there is a difference between a doctor's opinion regarding diagnosis and a doctor's opinion regarding etiology. Doctors "may testify to both [diagnosis and etiology] but the reliability of one does not guarantee the reliability of the other." Tamraz v. Lincoln Electric Co., 620 F.3d 665, 674 (6th Cir. 2010).

In this case, once the relevant question passes beyond diagnosis to causation, Dr. Vasey's opinion becomes much less strong.³² He does not have any special training in immunology, which is the most relevant discipline. See Terran v. Sec'y of Health & Human Servs., 195 F.3d 1302, 1316 (Fed. Cir. 1999) (stating that "[T]he rules of evidence require that the trial judge determine whether the testimony has a reliable basis in the knowledge and experience of the relevant discipline."). Although Dr. Vasey opined that the hepatitis B vaccine harmed Mr. D'Angiolini, Dr. Vasey struggled to articulate a theory about how the hepatitis B vaccine harmed him. Tr. 1555-61. Dr. Vasey eventually offered molecular mimicry. Tr. 1560. But, his knowledge about molecular mimicry was limited. Thus, his opinion about molecular mimicry was not persuasive. See Shapiro v. Sec'y of Health & Human Servs., 105 Fed. Cl. 353, 359 (Fed. Cl. 2012) (denying motion for review in relevant part and ruling that the special master was not arbitrary in finding that Dr. Shoenfeld failed to establish that molecular mimicry was a reliable theory to explain how the hepatitis B vaccine can cause chronic fatigue syndrome), aff'd without opinion, 503 Fed. Appx. 952 (Fed. Cir. 2013).

In addition to Dr. Vasey's relative unfamiliarity with the immunologic principles undergirding the theory of molecular mimicry, there is also a question about the information provided to Dr. Vasey. As alluded to earlier, Dr. Vasey was not Mr. D'Angiolini's treating doctor in 1997, when he received the hepatitis B vaccines. Mr. D'Angiolini did not start seeing Dr. Vasey until 2000, and, therefore, Dr. Vasey lacks any first-hand knowledge about Mr. D'Angiolini's health in the months following the vaccinations. Dr. Vasey did not contemporaneously see or evaluate Mr. D'Angiolini for his alleged vaccine-related symptoms and complaints. For this aspect of Mr. D'Angiolini's history, Dr. Vasey

³² On one occasion, a district court has excluded Dr. Vasey's testimony regarding causation as unreliable under Daubert. See Norris v. Baxter Healthcare Corp., 397 F.3d 878 (10th Cir. 2005) (affirming exclusion of evidence and grant of summary judgment); but see Hopkins v. Dow Corning Corp., 33 F.3d 1116, 1124-25 (9th Cir. 1994) (holding that district court did not abuse its discretion in admitting Dr. Vasey's testimony).

must rely upon Mr. D'Angiolini and his mother, who, by this time, were convinced that the hepatitis B vaccine harmed him.

The patient's subjective understanding that a vaccine harmed him is understandable. After all, petitioners in the Vaccine Program have been presumed to file their lawsuits alleging that a vaccine caused them some injury in good faith. See Grice v. Sec'y of Health & Human Servs., 36 Fed. Cl. 114, 121 (Fed. Cl. 1996). A potential problem is that patients may remember their histories inaccurately.

At Mr. D'Angiolini's initial appointment with Dr. Vasey, Mr. D'Angiolini provided a history. Since many of the details are important, it is set out at length.

[Mr. D'Angiolini] had been in good health until 03/97, at which point he was advised by his employer to have the hepatitis B vaccine. After the first injection he developed promptly some headaches and flu-like symptoms. These problems persisted over several weeks, and he received another vaccination in 04/97, "I was out of it." He was dragging himself to work. He could sleep for 24 straight hours. Apparently at that point, no one related these findings to the hepatitis B vaccination. Finally, in 10/97, he had a third injection as noted in the prescribed course. He had another reaction with chest pain, shortness of breath, sweats and worsening of his flu-like symptoms. By 11/97, he had been granted a short-term disability. He noted the 'brain fog' was severe. He saw a psychiatrist, who eventually concluded that he had an organic problem.

Exhibit 8 at 1.

Many statements in this history are not in accord with the Findings of Fact, which were based upon contemporaneously created medical records that were not available to Dr. Vasey. To start, Mr. D'Angiolini's description of himself as being in "good health" before the March 1997 vaccination leaves out much. Before the vaccination, he was seeing Dr. Middleman because his OCD was contributing to the breakup of his engagement and he was having headaches for which Dr. Middleman was prescribing medications. On the other hand, Mr. D'Angiolini was in "good health" in the sense that he was working at two jobs and did not have any physical impediments.

Mr. D'Angiolini's headaches are important. In 2000, he told Dr. Vasey that after the first vaccination he "developed promptly some headaches." Actually,

both Dr. Middleman's and Dr. Roman's notes show that Mr. D'Angiolini was complaining about and being treated for headaches before the vaccination.

Mr. D'Angiolini also told Dr. Vasey that after the first vaccination he developed "flu-like symptoms [that] persisted over weeks," apparently through the next vaccination in April 1997. Mr. D'Angiolini's recitation that he had "flu-like symptoms" in March or April 1997 was found not to be persuasive in the Findings of Fact.

Thus, the information available to Dr. Vasey in 2000 about Mr. D'Angiolini's health in 1997 was inaccurate. The history suggests a dramatic change from good health to a prompt multi-week persistence of flu-like symptoms. As determined in the Findings of Fact, Mr. D'Angiolini suffered from some problems, such as headaches, before the vaccination and his health did not decline drastically until months later. The differences between Mr. D'Angiolini's health before and after vaccination as found, on the one hand, in the Findings of Fact and, on the other hand, in Mr. D'Angiolini's history to Dr. Vasey in 2000, are significant.

In 2000, based in part on the inaccurate information given to him, Dr. Vasey formed an opinion that Mr. D'Angiolini "suffered an unusual immune mediated reaction to his Hepatitis B vaccine." Dr. Vasey communicated this opinion to the judge presiding over Mr. D'Angiolini's claim for workers' compensation benefits in a letter dated October 12, 2000. In this letter, Dr. Vasey wrote that an adverse reaction to the hepatitis B vaccine was recognized "at the case report level." As such, "well[-]intention[ed] honest physicians could contest my opinion." Dr. Vasey recommended an indefinite postponement of Mr. D'Angiolini's workers' compensation trial because of Mr. D'Angiolini's health and "to allow time for better understanding of the immunology and epidemiology of the vaccine reactions." Exhibit 133 at 23.

Dr. Vasey presented essentially this same opinion in his reports submitted for this litigation. Dr. Vasey's fundamental assumptions about Mr. D'Angiolini's health in 1997 did not change in the ensuing ten years. But, these assumptions were not supported by the Findings of Fact. Consequently, Dr. Vasey's opinion about causation, although well intended, cannot be credited. See Burns, 3 F.3d at 417.

B. Dr. Shoenfeld

Dr. Shoenfeld has a very impressive background in medicine, in general, and in immunology, more specifically. Within the specialty of immunology, Dr. Shoenfeld holds himself out as an auto-immunologist, meaning that he has focused on diseases in which the body's immune system attacks itself. Although the Secretary pointed out that "auto-immunology" is not a recognized sub-specialty in the sense that one could not seek treatment by an autoimmunologist as easily as with a rheumatologist, Tr. 1458-60, there is little doubt that if there were such a specialty, Dr. Shoenfeld would qualify.

Dr. Shoenfeld is listed as a contributing author in more than 1,000 articles appearing in peer-reviewed journals. His knowledge of the literature is encyclopedic. He spontaneously recalled articles reporting studies throughout his testimony. E.g. Tr. 1559.³³

Dr. Shoenfeld has been writing about the possibility that various vaccines cause autoimmune disease since 1996. See exhibit 85 at 65. Beginning in 2006, Dr. Shoenfeld has appeared in Vaccine Program cases to express an opinion that a vaccine caused the petitioner's injury. His participation in these cases contributed to Dr. Shoenfeld's conception of the entity he calls autoimmune syndrome induced by adjuvant (also known as "ASIA"). Dr. Shoenfeld's assertion that Mr. D'Angiolini suffers from ASIA is discussed at length below. See section VIII. Similarly, sections VI and VII, below, discuss Dr. Shoenfeld's assertion that Mr. D'Angiolini suffers from chronic fatigue syndrome and SLE.

Although Dr. Shoenfeld's knowledge about medical articles was detailed, Dr. Shoenfeld had a much less firm grasp on the medical records about Mr. D'Angiolini. For example, Dr. Shoenfeld was not sure that he reviewed Dr. Middleman's records. Tr. 1474. Dr. Middleman was the psychiatrist who was holding appointments with Mr. D'Angiolini in the six months before vaccination and for approximately a year after his third hepatitis B vaccination. Exhibit 24. As the best source for information about Mr. D'Angiolini's health during this critical time, Dr. Middleman's records are very important and underlie many of the

³³ While impressive, Dr. Shoenfeld's citation to articles that were not filed into the record can cause problems in a hearing as neither the Secretary's attorney nor the Secretary's expert witness can review those previously uncited articles.

Findings of Fact. As such, Dr. Shoenfeld should have certainly reviewed those records.

Dr. Shoenfeld's testimony suggested that he did not know Mr. D'Angiolini's medical history. Dr. Shoenfeld asserted that Mr. D'Angiolini had a "severe reaction" to the first dose of the hepatitis B vaccine. Exhibit 87 at 3. However, his report did not cite to any records documenting this "severe reaction," *id.*, and when cross-examined on this point, he also could not identify the basis for his assertion. Tr. 832-39. Dr. Shoenfeld further asserted that between April 18, 1997 and May 27, 1997, Mr. D'Angiolini did not complete his assignments at work. Tr. 840-41. But, the employer's record does not corroborate this assertion.

C. Dr. Lightfoot

Dr. Lightfoot graduated from medical school in 1961. He followed that education with more intensive focus on rheumatology. In addition to seeing patients, Dr. Lightfoot maintained an academic career, including many years as a professor at the Medical College of Wisconsin. For approximately one decade, he served as the chief of the rheumatology division for that institution. From Wisconsin, he moved to the University of Kentucky in 1987. There, he was a professor and the division director of allergy, immunology and rheumatology until 2003. Exhibit B at 2.

Consistent with his academic positions, Dr. Lightfoot has written approximately 40 articles appearing in peer-reviewed journals. He has also contributed chapters to books. The subject of most of his publications has been rheumatology. Exhibit B at 14-23.

As a rheumatologist, Dr. Lightfoot has seen many people who either have lupus or were suspected to have lupus. Tr. 1128 (approximately 30 percent of Dr. Lightfoot's 1,000 current patients have lupus). This background makes him well qualified to assess whether Mr. D'Angiolini has lupus. However, Dr. Lightfoot has relatively less experience in treating patients with chronic fatigue syndrome or OCD. See Tr. 1158, 1337, 1401-02. Consequently, his opinion with respect to those conditions cannot be given the same weight.

Dr. Lightfoot's background was the subject of intense questioning during voir dire. Mr. D'Angiolini's counsel's questions elicited testimony that Dr. Lightfoot had not studied vaccines or their possible adverse effects. Tr. 1081-90. These admissions led to an argument that Dr. Lightfoot was not qualified to

express an opinion on the ultimate question in this case, whether the hepatitis B vaccinations harmed Mr. D'Angiolini.

As Mr. D'Angiolini's counsel recognized, even if the objection to Dr. Lightfoot's qualification to opine about whether the vaccine caused Mr. D'Angiolini a disease were sustained, Dr. Lightfoot would remain qualified to testify about whether Mr. D'Angiolini suffered from a particular disease. See Tr. 1088-89. In this regard, Dr. Lightfoot stands in roughly the same shoes as Dr. Vasey, who expressed an opinion that a vaccine harmed Mr. D'Angiolini without testifying that he has studied vaccinations. The logical extension of Mr. D'Angiolini's argument is that only doctors who have studied immunology, maybe only doctors who have studied vaccinology, would be qualified to testify in Vaccine Program cases. This standard would excessively elevate the minimally acceptable qualifications.³⁴

Moreover, Dr. Lightfoot's experience seems to make him more qualified than Dr. Vasey to opine on immunologic topics. After the challenge to Dr. Lightfoot's background arose during voir dire, the Secretary elicited additional testimony. Dr. Lightfoot described how rheumatologists treat patients for diseases that are autoimmune in origin, including lupus. In addition, Dr. Lightfoot stated that he reviewed the articles cited by Dr. Shoenfeld and understood the immunologic concepts involved. Tr. 1121-28. Consequently, when Mr. D'Angiolini's attorney interposed objections to specific questions intending to elicit Dr. Lightfoot's opinion regarding causation, Mr. D'Angiolini's objection was overruled. See, e.g. Tr. 1194-98. Dr. Lightfoot's opinion was admitted and its worth will be weighed in sections below.

D. Dr. Whitton

Dr. Whitton was born in Scotland and obtained the equivalent of a medical degree in 1979. Five years later, he obtained a Ph.D. after studying herpes virus transcription.

In 1989, he joined the Scripps Research Institute in La Jolla, California. At that institution, he has taught neuropharmacology and immunology. He has acted

³⁴ Incidentally, this raised bar would probably cause more problems for petitioners, who bear the burden of proof, than for respondent.

as the editor of Virology since January 2006. In 2007, he declined an offer for a similar position for the Journal of Virology. He has written more than 160 articles published in peer-reviewed journals. Exhibit W at 2-12; Tr. 1600-03. After a presentation of his qualifications at the hearing on February 17, 2013, he was recognized as an expert in the areas of virology and immunology. Tr. 1603.

Dr. Whitton's testimony was relatively short because most of the issues on which he had opined had become moot.³⁵ His testimony focused on allergy and whether Mr. D'Angiolini was allergic to yeast. This topic was within the scope of his expertise.

The testimony of Doctors Vasey, Shoenfeld, Lightfoot and Whitton are discussed extensively in the following parts, which are organized by condition for which Mr. D'Angiolini seeks compensation. To restate, he claims a yeast allergy, chronic fatigue syndrome, lupus, and ASIA.

V. Yeast Allergy

Mr. D'Angiolini's claim about his allergy to yeast has fluctuated throughout this litigation. The ebbs and flows are, therefore, discussed in section A. At the end of the day, because Mr. D'Angiolini is putting forward a claim about yeast allergy, general information about yeast and typical allergic reactions is presented in section B. This foundation is the predicate for the conclusion, found in section C, that Mr. D'Angiolini did not establish that the yeast component in the hepatitis B vaccine caused an allergic reaction.

³⁵ As explained in the procedural history, in 2012, the Secretary retained Dr. Whitton to participate after Mr. D'Angiolini unexpectedly identified Dr. Buttram as a testifying witness in late 2011. Dr. Whitton's report directly responded to Dr. Buttram's opinions. See exhibit V. During the hearing, Mr. D'Angiolini's attorney announced that he was not going to call Dr. Buttram. Tr. 1590. The Secretary, however, maintained that she intended to call Dr. Whitton to testify concerning Mr. D'Angiolini's alleged yeast allergy. Tr. 1590-93.

A. Procedural History, including Experts' Opinions, Regarding Yeast Allergy

1. Initial Reports from Dr. Shoenfeld, Dr. Vasey, and Dr. Lightfoot

Dr. Shoenfeld's December 26, 2010 report about Mr. D'Angiolini specifically mentions that Mr. D'Angiolini has an allergy to yeast. Exhibit 87 at 3. This notation means that Dr. Shoenfeld was aware of this "fact." However, Dr. Shoenfeld did not identify yeast as a potential mechanism for an adverse reaction. His report focused on the causative role of the aluminum adjuvant. Id. at 7-8.

Unlike Dr. Shoenfeld who did not rely upon a yeast allergy, Dr. Vasey's initial report found the yeast allergy very important. Dr. Vasey stated that Mr. D'Angiolini "was known to be allergic to yeast." Exhibit 83 at 2 ¶ 4. Dr. Vasey did not identify the basis for this statement. Nevertheless, to Dr. Vasey, "the obvious explanation for Mr. D'Angiolini's reaction is the known yeast sensitivity documented at age 3 years." Id. at 3.

When Dr. Lightfoot responded to Dr. Vasey's report and Dr. Shoenfeld's report, Dr. Lightfoot carefully called into question the accuracy of the assertion that Mr. D'Angiolini was allergic to yeast. See exhibit A at 4-5, 18. Dr. Lightfoot's detailed review of the medical records justified revisiting the previous Finding of Fact on this issue.

Given the uncertainty about Mr. D'Angiolini's alleged yeast allergy, the undersigned sought supplemental information from Mr. D'Angiolini's experts about whether each thought Mr. D'Angiolini was allergic to yeast. Dr. Vasey's response was "I don't know. I would not recommend injecting him with yeast." Exhibit 96 at 2.

Dr. Shoenfeld's response was stronger. He dismissed the yeast allergy. He wrote:

The yeast allergy, if it exists, is not important for the claim of a long life CFS following the vaccine. Allergy is an acute condition, while the CFS after the [hepatitis B] vaccine is a chronic process and a chronic result. Mr. D'Angiolini does not have to be tested for yeast allergy. I believe that the case of the CFS [is] not due [to] yeast allergy but due to adjuvant effect.

Exhibit 97 at 1.

It appeared that these submissions put the alleged yeast allergy to rest. One of petitioner's experts, Dr. Vasey, stated that he did not know whether Mr. D'Angiolini was allergic to yeast. The other of petitioner's experts, Dr. Shoenfeld, stated that any yeast allergy "is not important." Mr. D'Angiolini seemed to agree with the view that the yeast allergy was not relevant. His initial pre-hearing brief, filed on January 5, 2012, did not use the term "yeast" at all.

2. Dr. Buttram's Report

Mr. D'Angiolini's submission of Dr. Buttram's report on January 6, 2012, brought the yeast allergy to the surface again. In reciting Mr. D'Angiolini's relevant medical history, Dr. Buttram referenced cytotoxic testing, exhibit 153 at 10, and a December 1, 2010 anti-saccharomyces cerevisiae antibody ("ASCA") test, id. at 6. Dr. Buttram emphasized the contribution of the yeast allergy by placing in bold the sentence stating "The presence of yeast allergy in [Mr. D'Angiolini's] case would have further intensified the allergic reaction." Id. at 21. Dr. Buttram's conclusion was:

My diagnoses in the case of Joseph D'Angiolini were:

Adverse reactions to Hepatitis B vaccines involving mercury and aluminum toxicities resulting in encephalitis, myocarditis, neuropathies, temporal arteritis, and chronic fatigue.

Yeast allergy is listed as a contraindication to hepatitis B vaccine administration in Physician's Desk Reference. Joe was allergic to yeast and tested positive for Anti Saccharomyces Cerevisiae Antibodies, the yeast that is in the Hepatitis B Vaccine. He should not have received this vaccine.

Id. at 29.

3. Developments after Submission of Written Reports

At this point, Mr. D'Angiolini's experts were not consistent. Mr. D'Angiolini's alleged yeast allergy was not significant to Dr. Shoenfeld and Dr. Vasey. But, the yeast allergy was the causative mechanism for Dr. Buttram. Mr. D'Angiolini's own position was not clear. Although Mr. D'Angiolini's attorney had filed Dr. Buttram's report at the request of his client and Ms. D'Angiolini, Mr.

D'Angiolini's attorney did not discuss yeast allergy in his Supplemental Prehearing Brief, filed on June 4, 2012.

During the January 3, 2013 pre-trial conference, the undersigned inquired about the yeast allergy. Mr. D'Angiolini's attorney intended to call Dr. Buttram, whose opinion relied upon the yeast allergy. In light of this representation, the undersigned filed, on January 9, 2013, two articles related to yeast allergy. Court exhibits 1004 and 1005.

Before Dr. Buttram testified, Mr. D'Angiolini called Dr. Shoenfeld. Dr. Shoenfeld's view was that yeast is one of four vaccine components that may trigger ASIA. Tr. 770-78, 803, 823. In support of his view, Dr. Shoenfeld cited a recently published article. Exhibit 197 (Maurizio Rinaldi et al., Anti-Saccharomyces cerevisiae Autoantibodies in Autoimmune Diseases: from Bread Baking to Autoimmunity, 45 Clinical Revs. Allergy Immunology 2 (2013)). This testimony prompted an objection from the Secretary. Mr. D'Angiolini's attorney and Dr. Shoenfeld explained that the submission of Court Exhibits 1004 and 1005 inspired Dr. Shoenfeld's theory with respect to how Mr. D'Angiolini's yeast allergy had harmed him. Tr. 774-75.

This explanation is confusing. Mr. D'Angiolini's alleged yeast allergy was a potential issue throughout the case. In March 2005, Mr. D'Angiolini indicated that because yeast is a component of the hepatitis B vaccine, an allergy to yeast may play a potential role in vaccine-caused CFS. Pet'r's Status Rep't, filed Mar. 14, 2005, at 4. The alleged allergy was mentioned in the Findings of Fact. Dr. Shoenfeld mentioned Mr. D'Angiolini's yeast allergy in his October 12, 2010 report. Exhibit 84. Dr. Shoenfeld, subsequently, stated that Mr. D'Angiolini's chronic fatigue syndrome was "not due [to] yeast allergy, but due to adjuvant effect." Exhibit 97 at 1. After this direct statement from Dr. Shoenfeld that the yeast allergy does not affect his opinion, it seems surprising that a special master's order would provoke additional reflection from Dr. Shoenfeld, given his decades of experience in immunology.

In any event, Dr. Shoenfeld's testimony was provided. Despite the ongoing dispute documented in the experts' supplemental reports and testimony, Mr. D'Angiolini's posthearing briefs do not discuss the validity of his yeast allergy claim. See Pet'r's Posthr'g Br.; see also Pet'r's Posthr'g Reply Br. In response to the Secretary's posthearing assertion that Mr. D'Angiolini's yeast allergy claim is not supported by evidence, Mr. D'Angiolini relies on the Findings of Fact alone without discussion of the subsequent record. Pet'r's Posthr'g Reply Br. at 1. In

accord with the Vaccine Act's directive for a special master to consider the record as a whole, 42 U.S.C. § 300aa—13(a)(1), the evidence regarding yeast is discussed. Topics include background information about yeast and Mr. D'Angiolini's medical history.

B. Basic Information about Yeast

The process of manufacturing the hepatitis B vaccine involves yeast. Genes from the hepatitis B virus that encode the hepatitis B surface antigen are inserted into common baker's yeast. The growth of the baker's yeast, also known as Saccharomyces cerevisiae, allows for the production of the hepatitis B surface antigen, which is the basis for the hepatitis B vaccine. Exhibit 1004 (Grotto) at 329-30; exhibit 1005 (DiMiceli) at 703.

However, “[a]s a result of biochemical and biophysical purification, there is no detectible yeast DNA and only trace amounts of yeast proteins (1-5%) in the final vaccine products.” Exhibit 1005 (DiMiceli) at 703; accord exhibit 1004 (Grotto) at 330. Nevertheless, one author stated that adverse reaction “may occur because of the minute quantities of yeast proteins present in the vaccine.” Exhibit 1004 at 333.³⁶ This possibility appears remote, at best, as the same author continued: “The potential of these proteins to induce a hypersensitivity reaction in primed individuals was examined by measuring of IgG and IgE antibody to yeast before and after three dose of vaccine. No significant increases occurred in most individuals and in those who experienced increases there was no correlation with clinical symptoms.” Id.

³⁶ The possibility that yeast might cause an adverse reaction is consistent with the package insert that notes that a hepatitis B vaccine is contraindicated for people with allergies to yeast. See exhibit 17 at 98 (excerpt from Physician's Desk Reference for Energix-B). However, a contraindication does not establish causality. See Werderitsh v. Sec'y of Health & Human Servs., No. 99-319V, 2005 WL 3320041, at *8 (Fed. Cl. Nov. 10, 2005), citing 21 C.F.R. § 600.80(l).

When people who are allergic to yeast encounter yeast, they most likely react within two days. Tr. 943 (Dr. Shoenfeld); cf. Tr. 1622 (Dr. Whitton describing most yeast allergies as a delayed type hypersensitivity reaction).

C. Mr. D'Angiolini's (Alleged) Allergy to Yeast

The best way to determine whether someone is allergic to yeast is to test the person with a reliable test. Mr. D'Angiolini has not identified any reliable test demonstrating an allergy to yeast.³⁷

Alternatively, a yeast allergy could be suspected, if not confirmed, by experience. See Tr. 943 (Dr. Shoenfeld "[T]he diagnosis of allergy should be done by the patient, not by a physician."). This appears to be the path taken by Mr. D'Angiolini.

Mr. D'Angiolini first suspected he was allergic to yeast when he was 10 years old and visiting Walt Disney World with his family. He ate a slice of pizza and vomited. From this episode, he concluded that he was allergic to yeast. Tr. 154; see also exhibit 51 at pdf 187-89 (May 31, 2002 W.C. Trial Tr. 49-51).³⁸

However, when Mr. D'Angiolini was asked about his relevant medical history in the course of seeking treatment, he did not include yeast on those forms. He did list other allergens, such as penicillin and sulfa. Exhibit 17 at 121-22 (letter

³⁷ Two tests, arguably, could show Mr. D'Angiolini's allergy to yeast. The first is a cytotoxic test for yeast that Dr. Buttram administered to Mr. D'Angiolini. Exhibit 43 at pdf 3. However, articles cited by Dr. Whitton convincingly demonstrate that a cytotoxic test is not a reliable test for allergies. Exhibit KK (Food and Drug Administration, Compliance Policy Guide Sec. 370.100 Cytotoxic Testing for Allergic Diseases (1985), available at <http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm123806.htm>); exhibit LL (I. Leonard Bernstein et al., Allergy Diagnostic Testing: An Updated Practice Parameter, 100.3 *Annals Allergy, Asthma & Immunology* S1 (2008)).

Second, during the hearing, Mr. D'Angiolini submitted a December 1, 2010 report showing the presence of ASCA to IgA and IgG. Exhibit 198. The experts were consistent that this test provided no information about whether Mr. D'Angiolini had an allergy, which is measured by IgE, to yeast. Tr. 1064-67, 1655.

³⁸ The attorney representing Mr. D'Angiolini's employer objected to allowing Ms. D'Angiolini to testify about an alleged yeast allergy because there was no testing for the allergy.

dated Sept. 13, 1998); exhibit 22 at pdf 4 (notes dated Nov. 17, 1998); exhibit 14 at 29 (questionnaire dated Oct. 6, 1999).

After Mr. D'Angiolini began pursuing compensation for his hepatitis B vaccination (either through a claim for workers' compensation or for Vaccine Program benefits), he began listing yeast among his allergies in histories provided to treating doctors. See exhibit 17 at 15 (Dr. Bray's Nov. 30, 1999 letter); exhibit 14 at 67 (letter dated Nov. 4, 1999, stating "yeast exposure gives him a headache"). In accord with the history that Mr. D'Angiolini gave to them, doctors sometimes included yeast allergies in their reports. These doctors, however, did not conduct any tests to confirm the allergy.

No persuasive evidence establishes that Mr. D'Angiolini suffered an adverse reaction to the yeast component in the hepatitis B vaccine. As discussed above, any allergic reaction to yeast would be apparent within approximately a few days of exposure. However, the evidence in this case does not persuasively establish that Mr. D'Angiolini was in ill health in the days immediately following any dose of the hepatitis B vaccine. As discussed in the context of the Findings of Fact, the parties disputed Mr. D'Angiolini's condition after vaccinations. Much of Mr. D'Angiolini's testimony was not credited because it was in either direct or indirect conflict with medical records created contemporaneously. In addition, even Mr. D'Angiolini did not claim that he had an immediate reaction.

D. Synopsis of Yeast Allergy

For these reasons, the record does not support a finding that Mr. D'Angiolini reacted adversely to the hepatitis B vaccine because of a yeast allergy. Therefore, to be entitled to compensation, Mr. D'Angiolini will need to pursue other avenues.

VI. Chronic Fatigue Syndrome

While the alleged yeast allergy was sometimes a less prominent part of Mr. D'Angiolini's case, his allegation that the hepatitis B vaccine caused him to suffer chronic fatigue syndrome has always been front and center. In 2004, Mr. D'Angiolini's attorney was promoting this case as the lead case about hepatitis B vaccine and chronic fatigue syndrome, although other cases involving the hepatitis B vaccine and chronic fatigue syndrome have proceeded separately. Mr. D'Angiolini and the Secretary presented extensive evidence about chronic fatigue syndrome.

The evidence relates to the following topics. First, there is information about what chronic fatigue syndrome is. See section VI.A. Second, this evidence is used to evaluate a fundamental aspect of Mr. D'Angiolini's claim, one which the parties strenuously disputed, whether Mr. D'Angiolini established that he suffers from chronic fatigue syndrome. See section VI.B. For the reasons explained therein, Mr. D'Angiolini did not establish this predicate. Nevertheless, the following two sections assume that Mr. D'Angiolini could proceed to the next steps in his claim. Thus, section C sets forth the well-established elements for a causation-in-fact claim and section D analyzes the evidence related to the three prongs of Althen.

A. Basic Information about Chronic Fatigue Syndrome

In the phrase "chronic fatigue syndrome," each term contributes to the meaning of the phrase. "Chronic" is defined as "persisting over a long period of time." Dorland's at 359. "Fatigue" has many meanings and interpretations. In this instance, it may best be described as a "loss of power or capacity to respond to stimulation." Id. at 685. A "syndrome" is a "set of symptoms that occur together." Id. at 1819; accord Tr. 1157. In chronic fatigue syndrome, the primary feature is, obviously, fatigue. To qualify as chronic fatigue syndrome, the fatigue must be accompanied by various other ancillary symptoms. Tr. 728, 1157-60. The associated symptoms are discussed in more detail in section VI.B.2(b), below.

Although reports of conditions resembling chronic fatigue syndrome date back many years, chronic fatigue syndrome became more widely known in the 1980s. Tr. 947-49. Many of the articles about chronic fatigue syndrome were published in that decade.

How many people are afflicted with CFS is a matter of some dispute. One study reported that the prevalence of CFS is between 0.4 and 2.0 per cent.³⁹ Exhibit 34 (O. Zachrisson et al., Immune Modulation with a Staphylococcal Preparation in Fibromyalgia/Chronic Fatigue Syndrome: Relation Between Antibody Levels and Clinical Improvement, 23 Eur. J. Clin. Microbiol. Infect. Dis. 98 (2004)) at 98. In the view of one attorney, chronic fatigue syndrome is "a source of considerable dispute within and beyond the medical community. Some

³⁹ "Prevalence" refers to "the number of cases of a disease that are present in a population at a specified time." Dorland's at 1513.

observers estimate that millions of CFS victims exist, but remain undiagnosed, while others remain unconvinced that CFS is anything more than a collection of symptoms of chronic depression.” Monique C.M. Leahy, Proof of Chronic Fatigue Syndrome and Fibromyalgia, 99 Am. Jur. Proof of Facts 3d 1, § 2 (2008).

B. Has Mr. D’Angiolini Established, by Preponderant Evidence, that He Suffers from Chronic Fatigue Syndrome?

A preliminary question is whether CFS is an appropriate diagnosis for Mr. D’Angiolini. One aspect of his case is to establish, by a preponderance of the evidence, that he actually suffers from a condition that he alleges was caused by a vaccine. Broekelschen, 618 F.3d at 1346.

When doctors diagnose a disease, the doctor evaluates the person’s signs and symptoms and compares them to the diagnostic criteria. Doctors involved in Mr. D’Angiolini’s care have gone through this process with Mr. D’Angiolini and reached inconsistent conclusions. Similarly, the doctors retained in this litigation have also come to different conclusions with respect to Mr. D’Angiolini’s diagnosis. Dr. Shoenfeld has opined that Mr. D’Angiolini suffers from CFS. Exhibit 97 at 3; Tr. 801, 828-29. In contrast, Dr. Lightfoot has opined that depression is a better diagnosis. Exhibit A at 14-15, 18; Tr. 1162.

1. Criteria

Diagnostic criteria help researchers understand a condition by promoting uniform case definition and case assessment. Without this common understanding, researchers in different disciplines may use different nomenclature, hindering progress in understanding the disease. This was certainly the case for chronic fatigue syndrome, which was given many different names. Exhibit 34 (M.C. Sharpe et al., A report – CFS: guidelines for research, 84 J. Royal Society of Medicine 118 (1991)) at 118.⁴⁰

By 1988, researchers proposed the name “chronic fatigue syndrome.” These same researchers attempted to define the condition, but their “definition proved to be unsatisfactory in practice.” Id. Other proposed definitions were also

⁴⁰ According to Dr. Shoenfeld, another name for CFS is “postvaccinal encephalitis.” Tr. 740. However, that term does not appear in the list given in the Sharpe article.

inadequate. Consequently, a group of interested British researchers met to propose “recommendations for the conduct and reporting of future studies of patients with chronic fatigue.” Id. at 119.

In 1994, an international chronic fatigue study group authored “a set of research guidelines for use in studies of the chronic fatigue syndrome.” Exhibit U (Keiji Fukuda et al., The Chronic Fatigue Syndrome: A Comprehensive Approach to Its Definition and Study, 121 Ann. Intern. Med. 953 (1994)) at 953. These guidelines are frequently referred to as either the Fukuda standards or the CDC standards because the lead author of the study, Dr. Fukuda, worked for the Centers for Disease Control and Prevention. Id. at 958. The Fukuda group drew upon the experience with the British guidelines, which are cited as reference 4 in the Fukuda article. Id. at 957.

The Fukuda criteria include both inclusionary and exclusionary factors (attached hereto as “Appendix A”). First, the person must suffer from “chronic fatigue,” meaning “self-reported persistent or relapsing fatigue lasting 6 or more consecutive months.” Exhibit U (Fukuda) at 954. This fatigue must be severe enough to cause a “substantial reduction in previous levels of occupational, educational, social, or personal activities.” Id. at 956; accord Tr. 960 (Dr. Shoenfeld). A more extensive explanation of fatigue appeared in the previous British guidelines. Among other points, the British researchers emphasized fatigue “is a subjective sensation and has a number of synonyms, including tiredness and weariness.” Exhibit 34 (Sharpe) at 120.

The subjective and self-reported nature of the fatigue continues to make diagnosing CFS a challenge for doctors. Dr. Shoenfeld explained that there is no laboratory test to diagnose CFS and that it is “very difficult to diagnose chronic fatigue syndrome.” Tr. 811.

Chronic fatigue, by itself, does not satisfy the diagnostic criteria for CFS. The person must also have “four or more of the following symptoms . . . concurrently present for ≥ 6 months: 1) impaired memory or concentration, 2) sore throat, 3) tender cervical or axillary lymph nodes, 4) muscle pain, 5) multi-joint pain, 6) new headaches, 7) unrefreshing sleep, and 8) post-exertion malaise.” Exhibit U (Fukuda) at 955. The inclusion of these ancillary features “generated the most disagreement” among the study group. The authors added that the controversy over the ancillary symptoms “underscores the need to establish

specific features of the chronic fatigue syndrome and the validity of any chronic fatigue syndrome case definition.” Id. at 957.⁴¹

When presented with chronic fatigue, the doctor was expected to evaluate the patient for “underlying or contributing conditions.” Exhibit U (Fukuda) at 954. For example, the doctor will test a person’s thyroid to see if it is underactive because an underactive thyroid can cause fatigue. If the person suffers from hypothyroidism, the doctor treats it. This patient, although suffering from chronic fatigue, would not fit the diagnostic criteria for CFS. Tr. 1158. Another example is chronic fatigue due to cancer. Tr. 862.⁴²

The more challenging question --- and the one that is more germane to Mr. D’Angiolini’s case --- is depression. “It is difficult to interpret symptoms typical of the CFS in the setting of illnesses such as major psychotic depression.” Exhibit U (Fukuda) at 957. Depression can make people feel fatigued. Tr. 1346. The Fukuda criteria tried to eliminate people with depression from the group of people satisfying the diagnostic criteria for CFS. Tr. 1161. Fukuda wrote that evaluating doctors should obtain a history that, among other things, “covers medical and psychosocial circumstances at the onset of fatigue [as well as] depression or other psychiatric disorders.” The doctor should examine the patient’s mental status with “[p]articular attention . . . directed toward current symptoms of depression or anxiety. . . . Evidence of a psychiatric or neurologic disorder requires that an appropriate psychiatric, psychological, or neurological evaluation be done.” Exhibit U (Fukuda) at 954.

In the Fukuda criteria, “[a]ny past or current diagnosis of major depressive disorder with psychotic or melancholic features” “exclude[s] a patient from the diagnosis of unexplained chronic fatigue.” Id. at 955. On the other hand, the list of conditions that do not exclude a CFS diagnosis includes “anxiety disorders, somatoform disorders, nonpsychotic or nonmelancholic depression.” Id. at 956.

⁴¹ Dr. Shoenfeld asserted that after the CDC released its criteria, the American College of Rheumatology revised the definition of chronic fatigue to eliminate the ancillary symptoms. Tr. 859-60, 865. But, later Dr. Shoenfeld agreed with the Fukuda criteria, including the inclusions of the ancillary symptoms. Tr. 964. In any event, Mr. D’Angiolini included the ancillary symptoms in his brief. Pet’r’s Posthr’g Br. at 5, citing Dorland’s at 1851.

⁴² In the transcript, the word “cancer” is incorrectly transcribed as “counsel.”

Dr. Lightfoot explained that separating the group of people with depression from the group of people with chronic fatigue syndrome is very difficult. Dr. Lightfoot pointed out that the common, at least partially successful, treatments for CFS are antidepressant medications. Tr. 1345-47.

Dr. Shoenfeld appears to share Dr. Lightfoot's view. Dr. Shoenfeld was listed as a co-author of a paper stating "some of the [Fukuda] criteria are difficult to interpret and opinions differ regarding the classification of chronic fatigue cases with a history of psychiatric illnesses." Exhibit 186 (Nicola Bassi et al., Chronic Fatigue Syndrome: Characteristics and Possible Causes for its Pathogenesis, 10 *Isr. Med. Assoc. J.* 79 (2008)) at 79. However, in his testimony, Dr. Shoenfeld seemed to indicate that a person could suffer from both depression and chronic fatigue syndrome. Tr. 819-20, 858-59.

2. Mr. D'Angiolini's Presentation

As set out above, the CFS criteria include two affirmative aspects, which are chronic fatigue and a mix of ancillary symptoms. Due to the prominence of fatigue in the diagnosis, Mr. D'Angiolini's symptoms relating to chronic fatigue are presented by themselves in section a below. The eight potential ancillary symptoms are collectively discussed in section b.⁴³

a) Chronic Fatigue

Determining whether Mr. D'Angiolini was sufficiently fatigued to meet this aspect of the CFS criteria involves two challenging factors. First, there is the definition of fatigue. Dr. Shoenfeld and Dr. Lightfoot consistently discussed that the fatigue involved in CFS is a fatigue so severe that, in Dr. Shoenfeld's analogy, a mother could not rise from bed to take her kindergartener to school. Tr. 753. The fatigue that most people experience from life's typical activities does not qualify as the fatigue present in chronic fatigue syndrome.⁴⁴ Tr. 849-50.

⁴³ In addition to these affirmative aspects, a diagnosis of CFS can be ruled out by a number of exclusionary factors, including "major depressive disorder." Exhibit U (Fukuda) at 955-56. This is discussed briefly in section 3 below.

⁴⁴ Dr. Lightfoot stated that Mr. D'Angiolini was fatigued "for some time before the vaccination." Tr. 1161. However, it appears that Dr. Lightfoot was not distinguishing between "ordinary" fatigue and severe fatigue.

Second, there is the challenge in figuring out what symptoms Mr. D'Angiolini experienced approximately 15 years ago. As discussed in the Findings of Fact, in October 1996, Mr. D'Angiolini "did not have any problems with being fatigued." The Findings of Fact mention places in the medical records where Mr. D'Angiolini is described as having problems with sleep, drinking coffee, and reporting tiredness. For example, on March 24, 1997, Mr. D'Angiolini told Dr. Middleman that he was sleeping 15 hours a day. Exhibit 24 at 10. When this record was called to Dr. Shoenfeld's attention, Dr. Shoenfeld stated this episode was not the start of Mr. D'Angiolini's CFS because it "was one event." Tr. 974; but see Tr. 849 (Dr. Shoenfeld listing sleeping 16 hours as one factor contributing to Mr. D'Angiolini's diagnosis of CFS).

Around this time when Mr. D'Angiolini reported he slept for 15 hours in one day, he was working two jobs. He was maintaining his job as a mental health technician at Valley Forge Medical Center and Hospital and his evaluation from this time indicated that he was performing very well. Exhibit 16 at 31-32.⁴⁵ In addition, he was also teaching guitar on a part-time basis, usually working on Saturdays and Sundays at Bachman's Music Store. Exhibit 16 at 304-12.

Mr. D'Angiolini's employment history solves both challenges listed above. First, Fukuda defined the fatigue in CFS as one debilitating enough to cause a "substantial reduction in previous levels of occupational, educational, social, or personal activities." Exhibit U (Fukuda) at 956. In line with this limitation, Dr. Shoenfeld listed not going to work and not playing music as factors contributing to Mr. D'Angiolini's diagnosis for chronic fatigue syndrome. Tr. 848-49; see also Tr. 1058 (Mr. D'Angiolini was functioning before the vaccines because he was "a very productive person"). When questioned about the Fukuda definition of fatigue, Dr. Lightfoot, too, stated that he would look to when Mr. D'Angiolini lacked the strength "to go out and compete in the marketplace or engage in his hobbies." Tr. 1347.⁴⁶

⁴⁵ Dr. Shoenfeld assumed that Mr. D'Angiolini was not completing his assignments at work because he was tired. Tr. 841. But, Mr. D'Angiolini's employer's records do not support that assumption. Exhibit 16 at 31-32.

⁴⁶ Although Dr. Middleman was not speaking about Fukuda's definition of fatigue, she stated "when someone is unable to work, and that suggests a change in the level of functioning[,] that change [in function] has to be accounted for in some way." Tr. 49.

Second, unlike the accuracy of a psychiatrist's record, which depends largely on the historian's ability to recall what has happened, Mr. D'Angiolini's employment records are objective. These records show that Mr. D'Angiolini worked at both Valley Forge Medical Center and the music store until November 5, 1997. Findings of Fact at 33, citing exhibit 51 at pdf 18 (June 7, 2001 W.C. Trial Tr. 6); exhibit 53 ¶ 11; exhibit 16 at 311.

Consequently, the sudden reduction of Mr. D'Angiolini's employment occurred at the beginning of November 1997. The reason for the decrease in activities is not entirely clear. Dr. Middleman's notes from November 5, 1997, mention sporadic suicidal feelings for four months, visits with prostitutes, not taking care of his apartment, and not changing his clothes. Her notes do not mention any problem with fatigue, tiredness, or lethargy. Exhibit 24 at 13.

The next day, Mr. D'Angiolini's mother brought him to her physician, Dr. Bray. Dr. Bray's entry for this day, which is typed, states that Mr. D'Angiolini complained about "extreme fear, . . . chest pain, [shortness of breath], palpitations, [and] dizziness." Dr. Bray diagnosed Mr. D'Angiolini as suffering from "Severe Depression" and prescribed amitriptyline and Valium. Exhibit 61. Again, Dr. Bray's notes, which appear to be created contemporaneously with the appointment, do not indicate that Mr. D'Angiolini was complaining about fatigue, etc.⁴⁷ Moreover, Dr. Shoenfeld acknowledged that agoraphobia, suicidal ideation, and panic attacks are not symptoms of chronic fatigue. Tr. 867.

Another confounding piece of evidence regarding Mr. D'Angiolini's fatigue is a report from April 1998, when Mr. D'Angiolini went to a local emergency room for a long duration headache with occasional nausea, photophobia, and chest pain. Exhibit 15 at 12. He informed his doctors that he was "active" and "runs." Id.; see also Findings of Fact at 33. Dr. Shoenfeld, apparently unaware of this record, declared "[s]omebody with chronic fatigue will not play basketball. . . . He will not run five kilometers." Tr. 1461.

⁴⁷ More than two years later, Dr. Bray wrote a letter in support of Mr. D'Angiolini's claim for medical leave benefits. In 1999, Dr. Bray stated that "[d]ue to the extreme fatigue he was not able to care for himself or his environment." Exhibit 17 at 15. Similarly, two more years later, Dr. Bray wrote another letter in support of Mr. D'Angiolini's claim for disability benefits. Dr. Bray repeated that Mr. D'Angiolini "reported sleeping up to 16 hours a day and still feeling fatigued." Exhibit 131 (letter dated May 9, 2002).

These factors make determining when Mr. D'Angiolini started having severe fatigue difficult. Dr. Shoenfeld's testimony about playing basketball is tantamount to a concession that Mr. D'Angiolini was not suffering chronic fatigue (let alone chronic fatigue syndrome) in April 1998.⁴⁸

On October 10, 1998, Mr. D'Angiolini saw Gregory Bach, whose letterhead states that he is board certified in family medicine and addiction medicine. Exhibit 5 at 21. Dr. Bach's handwritten notes, which are difficult to decipher, indicate that Mr. D'Angiolini's chief complaints included "sweats, [weight] gain, heart palpitations, twitching, headache, neck stiffness, light sensitivity, light head, confusion, [difficulty with] speech, mood swings, depression." Dr. Bach's impressions included: "1. Fibromyalgia, 2. Chronic fatig. 3. Myopathy." *Id.* at 26. This October 10, 1998 reference to chronic fatigue appears to be the earliest reference to this symptom in Mr. D'Angiolini's medical records. *See* Tr. 1281.

Dr. Shoenfeld made two inferences from Dr. Bach's recitation of "chronic fatig." First, Dr. Shoenfeld understood that the chronic fatigue must have been present for at least several months. If the fatigue had a shorter duration, the doctor would have said "tiredness of one or two days." Tr. 842. Second, in Dr.

⁴⁸ Mr. D'Angiolini's briefs shed little light on this topic. For example, Mr. D'Angiolini's supplemental prehearing brief, which was filed in response to an order seeking further support for the disputed diagnoses, fails to discuss fatigue. Instead, the supplemental brief lists the ancillary symptoms only. Pet'r's Suppl. Prehr'g Br., filed June 4, 2012, at 3-4.

In Mr. D'Angiolini's posthearing brief, to support the assertion that he had fatigue, Mr. D'Angiolini cites to a portion of Dr. Shoenfeld's testimony in which Dr. Shoenfeld was responding to questions from the undersigned. Pet'r's Posthr'g Br., filed May 21, 2013, at 6, citing Tr. 961-75. The portion of these 14 pages that is most specific about the onset of Mr. D'Angiolini's fatigue is still quite vague:

THE COURT: Okay. So, if we use a definition of fatigue that results in substantial reduction in previous levels of occupational, educational, social and personal activities, so significant fatigue, when did Mr. D'Angiolini start having fatigue?

THE WITNESS: I believe that it was definitely after the vaccines. If I will recall well, it was after the second vaccine, but don't catch me in my word, but definitely it was after the vaccines.

Tr. 961.

Shoenfeld's opinion, Dr. Bach's use of "fatig." is an abbreviation for chronic fatigue syndrome. Tr. 852-53.

Following the visit with Dr. Bach, Mr. D'Angiolini went to the Penn Center for Healing, where Dr. Anne Norris saw him. His chief complaint was "fatigue." The history Dr. Norris obtained recounts that Mr. D'Angiolini had "sudden onset fatigue" in late June 1997. Her record indicates that Mr. D'Angiolini has "been out of work for a year [secondary to] fatigue."⁴⁹ Dr. Norris created a series of notes, corresponding to the ancillary symptoms associated with CFS. For example, she stated that Mr. D'Angiolini did not get refreshing sleep, did get headaches, but did not have either joint symptoms or muscle pain. Dr. Norris's impression was "not CFS by criteria." Exhibit 22 at 4 (Nov. 17, 1998).

On November 10, 1998, Dr. Roman saw Mr. D'Angiolini at the East Norriton Family Practice. Mr. D'Angiolini was complaining about fatigue. Exhibit 23 at 32; see also exhibit 50 at pdf 268-72 (Roman Dep. Tr. 29-33). Dr. Roman ordered more tests and also referred Mr. D'Angiolini to Dr. Buttram as well as other doctors. Exhibit 50 at pdf 312 (Roman Dep. Tr. 73).

One of the doctors to whom Dr. Roman referred Mr. D'Angiolini was a cardiologist, Dr. Weber. Mr. D'Angiolini told Dr. Weber that, for one year, he was having "dyspnea on exertion when he is doing a strenuous exercise such as heavy lifting or walking while carrying a heavy parcel." Exhibit 6 at 17 (record dated Nov. 13, 1998). This report implies that Mr. D'Angiolini was exercising, meaning that it is unlikely that he was having the fatigue associated with chronic fatigue syndrome. Dr. Weber's record does not mention fatigue.

b) Ancillary Symptom Overview

As previously stated, the Fukuda guidelines list eight other problems of which four are necessary to establish a diagnosis of CFS. Fukuda qualifies this general list of problems in two respects. The first limitation is that all of the symptoms "must have persisted or recurred during 6 or more consecutive months of illness." Exhibit U (Fukuda) at 954. The second qualification is that the symptoms "must not have predated the fatigue." Id. at 956.

⁴⁹ This history is not entirely consistent with the Findings of Fact.

(1) Ancillary Symptom #1: Impaired Memory or Concentration

Mr. D'Angiolini identified ten records listing memory or concentration as a problem. Pet'r's Suppl. Prehr'g Br. at 3-4. The earliest of these records was created on October 6, 1999. Exhibit 14 at 21-22.⁵⁰

The Secretary asserts that Mr. D'Angiolini began seeing Dr. Middleman before the vaccinations for various problems, including "problems with his memory." Resp't's Posthr'g Br. at 2, citing Findings of Fact 17-22 and exhibit 24 at 5-8.

(2) Ancillary Symptom #2: Post-exertional Malaise

Mr. D'Angiolini has identified more than 10 medical records that, in his view, indicate that he suffered from post-exertional malaise. Pet'r's Suppl. Br., tab B, at 2. Although Mr. D'Angiolini cited the November 10, 1998 visit with Dr. Roman during which Mr. D'Angiolini complained about fatigue, Dr. Roman's notes do not indicate a problem with post-exertional malaise. See exhibit 23 at 32. Dr. Weber's November 13, 1998 record does refer to post-exertional malaise by indicating that Mr. D'Angiolini had shortness of breath after strenuous activities. Exhibit 6 at 17.

About one year later, which is after Mr. D'Angiolini began seeking compensation in the Workers' Compensation proceeding and in the Vaccine Program, he reported to doctors problems with fatigue after exertion. E.g. exhibit 14 at 22 (record dated Oct. 6, 1999, stating "Have no energy to do anything. If I do something[,] for 4 days after I'm wiped out"); exhibit 36 at 15-18 (record dated Oct. 6, 1999, from Dr. Buttram).

(3) Ancillary Symptom #3: Unrefreshing Sleep

Reports of unrefreshing sleep appear throughout Mr. D'Angiolini's medical records. On three occasions in February 1999, which is before he received the first

⁵⁰ As discussed previously, in 1999 and 2002, Dr. Bray wrote letters indicating that Mr. D'Angiolini had memory or concentration problems going back to November 6, 1997. However, Dr. Bray's notes from November 6, 1997 do not reflect problems in memory or concentration.

dose of the hepatitis B vaccine, Mr. D'Angiolini told Dr. Middleman about problems with his sleeping. Exhibit 24 at 9-10.

He also told Dr. Middleman about problems with sleeping after the vaccinations. Exhibit 24 at 10-15. When Mr. D'Angiolini saw Dr. Roman in November 1998, he reported lengthy sleeping since summer 1997. Exhibit 23 at 32.

(4) Ancillary Symptom #4: Muscle Pain

On May 22, 1997, Mr. D'Angiolini told Dr. Middleman that he was having "body aches." Exhibit 24 at 11; Tr. 30. This may have been an isolated instance as Dr. Middleman's records do not report more complaints of muscle pain.

More frequent reports of muscle pain start toward the end of 1999. On October 6, 1999, Mr. D'Angiolini's chief complaint to Dr. Buttram included "constant joint and muscle pain." Exhibit 36 at 15. Dr. Bray listed "aches and pains" in his November 30, 1999 letter. Dr. Waisbren's December 13, 1999 letter mentioned, among other problems, "muscle pains." Exhibit 21 at 9.

(5) Ancillary Symptom #5: Joint Pain

The reports about muscle pain from 1999 overlap with reports of joint pain.

(6) Ancillary Symptom #6: Headaches of a New Type or Severity

As discussed in the Findings of Fact, Mr. D'Angiolini had headaches before his vaccination. His psychiatrist, Dr. Middleman, was prescribing medications to help with his headaches.

Mr. D'Angiolini also experienced headaches after vaccination. See exhibit 23 at 32. However, Mr. D'Angiolini has not persuasively established that the headaches were of a new type or severity.

(7) Ancillary Symptom #7: Sore Throat that is Frequent or Recurring

For this feature Mr. D'Angiolini identified only records from his October 6, 1999 visit with Dr. Buttram. Pet'r's Suppl. Prehr'g Br., tab B, at 3. The list of

chief complaints included “intermittent sore throat.” Exhibit 14 at 22. Dr. Buttram’s handwritten notes repeat this problem. Exhibit 36 at 18.

These records appear isolated. For the December 9, 1999 visit with Dr. Waisbren, there is a no check for sore throat. Exhibit 20 at 21. Dr. Bray’s November 30, 1999 letter does not include sore throat.

(8) Ancillary Symptom #8: Tender Cervical or Axillary Lymph Nodes

Like the sore throat symptom just discussed, the only references cited by Mr. D’Angiolini come from the October 6, 1999 visit with Dr. Buttram. Again, these mentions stand in isolation. Dr. Waisbren did not find any problem with Mr. D’Angiolini’s lymph nodes. Exhibit 20 at 23. When Mr. D’Angiolini visited the Cleveland Clinic in 2004, Dr. Gorenssek found “no significant adenopathy.” Exhibit 37 at 22.

3. Assessment of the Evidence

Mr. D’Angiolini’s assertion that he has CFS suffers from many shortcomings. Primarily, there is a problem determining when his fatigue began. The lack of clarity on this point is a significant flaw because CFS is a disease about fatigue.

Mr. D’Angiolini occasionally linked his abrupt cessation of employment in early November 1997, to fatigue. However, when Mr. D’Angiolini saw doctors in November and December 1997, he described other problems but not fatigue. Furthermore, his running in April 1998, as reflected in the visit to the emergency room, shows that he was capable of sustained physical exercise. Exhibit 15 at 12.

Mr. D’Angiolini’s ability to exercise further complicates the assessment of medical records created in the latter half of 1998, when he saw Doctors Bach, Roman, Norris, and Weber. While Mr. D’Angiolini sometimes reported he was having fatigue, he also reported that the fatigue (or shortness of breath) was associated with strenuous activities. Among these doctors, Dr. Norris appears to have been especially solicitous about the possibility that Mr. D’Angiolini suffered from CFS because her notes present information about not only Mr. D’Angiolini’s

fatigue but also the ancillary symptoms associated with CFS. Her conclusion that Mr. D'Angiolini was not suffering from CFS, therefore, is very valuable.⁵¹

If Mr. D'Angiolini were given the benefit of the doubt that his chronic fatigue began in July 1998, he would still need to establish that he suffered from four of eight ancillary symptoms to meet the criteria for CFS.⁵² As summarized in the chart below, Mr. D'Angiolini has at least a viable argument for one or two symptoms, depending on when the fatigue started. If his fatigue began in July 1998, then the post-exertional malaise started around the same time but his muscle pain and joint pain started more than a year later. On the other hand, if Mr. D'Angiolini's fatigue began around October 1999, then the post-exertional malaise would have pre-dated the fatigue and no longer qualifies as a supporting symptom.

Symptom	Assessment	Supporting CFS Diagnosis?
Impaired Memory	Existed before vaccination and before fatigue	No
Post-exertional Malaise	Started around August 1998	Possibly
Unrefreshing Sleep	Existed before vaccination and before fatigue	No

⁵¹ Dr. Norris's affirmative statement that Mr. D'Angiolini did not meet the diagnostic criteria for CFS is more persuasive than Dr. Bach's statement on which Mr. D'Angiolini relies. See Pet'r's Posthr'g Br. at 6 (citing Dr. Bach as one treating doctor who diagnosed Mr. D'Angiolini with CFS). First, strictly speaking, Dr. Bach's notation of "chronic fatig." is ambiguous because it could mean "chronic fatigue" or "chronic fatigue syndrome." Second, there is little information in Dr. Bach's own record to support a determination that Mr. D'Angiolini suffered from four of the eight ancillary symptoms needed for a diagnosis of chronic fatigue syndrome. Third, Dr. Bach includes "depression" as one of Mr. D'Angiolini's chief complaints. Depression can exclude the diagnosis of chronic fatigue syndrome.

⁵² If Mr. D'Angiolini's chronic fatigue began in July 1998, this date would be approximately nine months after his third and final dose of the hepatitis B vaccine in October 1997. Pursuant to the third prong of Althen, Mr. D'Angiolini would be required to show that nine months is an appropriate interval to infer causation.

Muscle Pain	Started around October 1999	Possibly
Joint Pain	Started around October 1999	Possibly
Headaches	Existed before vaccination and before fatigue	No
Sore throat	Insufficient evidence	No
Tender lymph nodes	Insufficient evidence	No

The lack of corroborating ancillary symptoms is significant because not all cases of “chronic fatigue” qualify as “chronic fatigue syndrome.” See Lombardi, 656 F.3d 1354 (finding special master was not arbitrary in rejecting petitioner’s claim that she suffered from chronic fatigue syndrome). Dr. Shoenfeld recognized the challenges in fulfilling the actual diagnostic criteria for chronic fatigue syndrome when he, as a co-author, wrote “only about 1% of patients who are given the diagnosis in primary care settings meet the criteria for CFS.” Exhibit 186 (Bassi) at 79.

Finally, because Mr. D’Angiolini has not persuasively demonstrated that he fits the affirmative portion of the CFS diagnostic criteria, examining the relevant exclusionary factors is not needed. This aspect would be particularly challenging because the Fukuda article distinguishes between “major depressive disorders,” and “nonpsychotic or nonmelancholic depression.” The former exclude the diagnosis of CFS while the latter permits the diagnosis. Exhibit U (Fukuda) at 955-56. Whether Dr. Lightfoot, who is a rheumatologist, possesses the requisite experience to opine on which side of this line Mr. D’Angiolini falls is quite uncertain.

Mr. D’Angiolini’s failure to present preponderant evidence that he suffers from CFS precludes an award of compensation based upon this disease. See Broekelschen, 618 F.3d at 1350. In this circumstance, Mr. D’Angiolini has not established that he does in-fact, suffer from CFS. See Lombardi, 656 F.3d at 1352. Nevertheless, an examination of the Althen factors may promote judicial efficiency.

C. Standards for Adjudicating a Causation-in-Fact Claim

If Mr. D'Angiolini had established that he suffered from CFS, his burden would be to show that the hepatitis B vaccines were the cause in fact of his CFS. The Federal Circuit set forth the elements of a causation-in-fact case in Althen: “(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury.” Althen, 418 F.3d at 1278.

D. Althen Analysis for Chronic Fatigue Syndrome

Each of the three prongs of Althen is discussed in separate sections, beginning with the first prong, below. For purposes of organizational clarity, the third prong precedes the second prong.

1. Prong 1 of the Althen Analysis

The first prong of Althen attempts to determine the general question of whether a vaccine can cause a particular injury. See Pafford v. Sec'y of Health & Human Servs., 451 F.3d 1352, 1356 (Fed. Cir. 2006) (affirming special master's use of “can cause” and “did cause” as consistent with the Althen test); Veryzer v. Sec'y of Health & Human Servs., 100 Fed. Cl. 344, 352 (2011) (describing the first prong of Althen as presenting the question of general causation). Any discussion about the causes of chronic fatigue syndrome is challenging because, at the most basic level, doctors do not know any cause for CFS. Tr. 869 (Dr. Shoenfeld). (The medical term for an unknown cause is “idiopathic.” Dorland's at 912.)

In his testimony, Dr. Shoenfeld stated that cases of CFS have developed after an infection. Tr. 728. That testimony is accord with Dr. Shoenfeld's November 30, 2005 report. There, he listed several viruses (the Epstein-Barr virus, cytomegalovirus, HHV-6, enterovirus, parvovirus) and several bacteria (mycoplasma, Borrelia, C. pneumonia) as “pathogens known to be involved” in causing CFS. Exhibit 31 at 6. During his testimony, when he was asked about these infectious agents, Dr. Shoenfeld stated he still thinks that the Epstein-Barr virus causes CFS. However, for the remaining items on the list (except possibly the parvovirus), Dr. Shoenfeld averred that they were only “claimed in the literature.” Dr. Shoenfeld stated that for these other infectious agents, there was “no stringent evidence,” “no epidemiological studies and definitely no[] experimental models.” Tr. 960. Dr. Shoenfeld commented that the suggestion that

enterovirus causes CFS was offered “when you didn’t know what happens.” Tr. 959.

Into this mix of potential causative factors, Dr. Shoenfeld added the hepatitis B vaccine. Exhibit 31 at 7; exhibit 87 at 6. At hearing, Dr. Shoenfeld advanced a theory in which the adjuvant in the vaccine (alum) is deposited into the muscles.⁵³ He stated “aluminum definitely is one of the main causes to be blamed in [Mr. D’Angiolini’s] condition.” Tr. 766; accord Tr. 821. Dr. Shoenfeld appears to have proposed alternative paths for the aluminum after it enters the muscle. First, the aluminum damages the “muscle fibers thus the chronic fatigue.” Second, the particles of aluminum diffuse to the brain and cause “the neurologic complications (i.e. sleep disturbances, cognitive impairments, etc.).” Exhibit 97 at 3.

For the opinion that aluminum may stay in the muscles into which the vaccine is administered, Dr. Shoenfeld has support. The articles from France about macrophagic myofasciitis indicate that muscle biopsies have shown the presence of aluminum years after vaccination. See exhibit 108 (R.K. Gherardi et al., Macrophagic myofasciitis: an emerging entity, 352 *Lancet* 347(1998)); exhibit 109 (R.K. Gherardi et al., Macrophagic myofasciitis lesions assess long-term persistence of vaccine-derived [aluminum] hydroxide in muscle, 124 *Brain* 1821 (2001)) at 1826; exhibit S (T. Papo, Macrophagic myofasciitis: focal or systemic?, 70 *Joint Bone Spine* 242 (2003)) at 244. Dr. Lightfoot agreed: some people “have aluminum at the deposit, no surprise, where the aluminum was injected months or weeks or years before.” Tr. 1184. The question is do the people whose muscle contain aluminum develop CFS?

Here, the evidence is much more sparse. None of the experts discussed any articles reporting the symptoms of people with macrophagic myofasciitis.

In addition to opining that aluminum in muscles causes chronic fatigue, Dr. Shoenfeld also stated that the aluminum leaves the muscles and is diffused, via the blood, to the brain. In the brain, the aluminum impairs the neurologic functions. Exhibit 97 at 3; Tr. 767. Early in Dr. Shoenfeld’s testimony, he stated that he did

⁵³ Dr. Shoenfeld disclosed this theory in his reports before the hearing. See exhibit 87 at 8; exhibit 95 at 2; exhibit 97 at 3. His reports also presented other theories, such as molecular mimicry. However, Mr. D’Angiolini is asserting only an adjuvant theory. See Pet’r’s Postthr’g Br. at 9-10; Pet’r’s Reply Br. at 9-10.

not have any evidence that the aluminum actually reaches the brain. It was “conceivable.” Tr. 768.

Later, Dr. Shoenfeld was presented with a paper, which he had cited in his reports, that “support[s] everything” that Dr. Shoenfeld had said earlier. Tr. 1009, discussing exhibit 107 (K. Redhead et al., “Aluminium-Adjuvanted Vaccines Transiently Increase Aluminum in Murine Brain Tissue, 70 Pharmacology Toxicology 278 (1992)). The Redhead paper showed that aluminum from vaccines causes a transient rise in the amount of aluminum in brain tissue of mice. Exhibit 107 at 279. The mice, however, did not become sick. Id.; see also Tr. 1012-13.

Dr. Lightfoot was skeptical about the proposition that aluminum is deposited into the brain. Dr. Lightfoot explained that aluminum, like other minerals, circulates in the bloodstream and part of this passage takes place in the brain. Tr. 1184, 1375-76. Dr. Lightfoot asserted that no one has shown that aluminum “deposits in the brain and inflames the brain.” Tr. 1184; see also Tr. 1190-91; cf 1485 (Dr. Shoenfeld did not know whether the aluminum would be in the brain as a particle). Furthermore, any deposit of aluminum into the brain would need to exceed the physiologic level, which corresponds to the amount of aluminum in the brain from other sources. See exhibit 101 (Robert A. Yokel et al., Aluminum bioavailability from basic sodium aluminum phosphate, an approved food additive emulsifying agent, incorporated in cheese, 46 Food Chemical Toxicology 2261 (2008)) (discussing aluminum available to the body from food and water).

To counter Dr. Shoenfeld’s theory that the hepatitis B vaccine can cause CFS, Dr. Lightfoot cited an article from Canada. Exhibit A at 20 (reference 15). In this report, the researchers obtained information about people who reported that they experienced chronic fatigue after receiving a hepatitis B vaccination. The researchers identified 30 people who fit the standard definition for CFS, including the lack of an alternative explanation for the fatigue. Most people reported that their chronic fatigue began within three months of their vaccination.

The researchers found that “there was no evidence linking hepatitis B administration and the appearance of CFS.” Exhibit Q (Gilles Delage et al., Report of the Working Group on the Possible Relationship between Hepatitis B Vaccination and the Chronic Fatigue Syndrome, 149 Can. Med. Ass. J. 314 (1993)) at 315. They provided five reasons for this conclusion. Because of their finding, the researchers concluded that additional research about a causal connection between the hepatitis B vaccine and CFS should be undertaken only if postmarketing surveillance suggests such a relationship. Id. at 316.

Dr. Lightfoot's testimony on direct examination about this article was less than one page. In short, he stated that the researchers looked for an association between the hepatitis B vaccine and CFS and did not find one. Tr. 1168. Dr. Lightfoot later opined that this work was analogous to reports that the Institute of Medicine creates. Tr. 1403-05.

On the other hand, Dr. Shoenfeld was very critical of the article. He pointed out that the Canadian researchers did not conduct an experiment, meaning they did not inject animals with a vaccine to see what happens. In addition, he suggested that the authors, whose names he did not know, may have reported the results inaccurately because the authors were influenced by either monetary concerns or a fear of reducing the rate of vaccination. Tr. 871-72.

Dr. Shoenfeld's criticisms miss their mark. The attack on the integrity of the researchers lacked any basis. Moreover, the Canadian researchers compared the incidence of people who received the hepatitis B vaccine and, thereafter, developed chronic fatigue syndrome with the incidence of people who received the hepatitis B vaccine but did not develop CFS. Dr. Shoenfeld did not opine that this method of study was not a legitimate basis for conducting an epidemiologic study. Although the Canadian researchers did not experiment on animals, animal studies are not the only method useful in investigating causal relationships.

The evidence surrounding Dr. Shoenfeld's theory that an adjuvant can cause CFS does not support finding the theory reliable. The starting point is that there is no medical knowledge of the cause or causes of CFS. Factors that Dr. Shoenfeld identified as "known" to be associated with CFS in 2005, are no longer accepted. Dr. Shoenfeld's adjuvant theory may turn out to be another example, to use his words, of "theories [proposed] when you didn't know what happened." Tr. 959.

Dr. Shoenfeld's adjuvant theory may have some biologic plausibility in that the macrophagic myofasciitis studies present some basis for finding that aluminum from a vaccine may persist in the muscle. However, the persistence of aluminum does not persuasively explain why the person would suffer chronic fatigue (let alone the ancillary symptoms, such as a loss of memory or headaches). Dr. Shoenfeld's assertion that the aluminum also goes to the brain is not reliable. Dr. Lightfoot's opinion that the aluminum from a vaccine would not (or maybe could not) enter the brain in levels that are physiologically relevant was more persuasive than Dr. Shoenfeld's opinion that it might. This aspect of Dr. Shoenfeld's theory seems particularly lacking in reliable support.

Finally, the Canadian epidemiological study further undermines the conclusion that the hepatitis B vaccine can cause CFS, regardless of the mechanism involved. This study, while not perfect, found that the hepatitis B vaccine was not associated with causing CFS.

For all these reasons, Mr. D'Angiolini has not met his burden of establishing the persuasiveness of Dr. Shoenfeld's theory.⁵⁴ His opinion was not reliable. See Moberly, 592 F.3d at 1324 .

2. Prong 3 of the Althen Analysis

If Mr. D'Angiolini suffered from CFS and if there were a reliable theory to explain how the hepatitis B vaccine can cause CFS, the next step would be to determine the amount of time that is medically appropriate to infer causation. Bazan, 539 F.3d at 1352; Shapiro v. Sec'y of Health & Human Servs., 101 Fed. Cl. 532, 542-43 (2011), reconsideration denied after remand, 105 Fed. Cl. 353 (Fed. Cl. 2012), aff'd without opinion, 503 Fed. Appx. 952 (Fed. Cir. 2013). To prevail, Mr. D'Angiolini would also need to establish that the first manifestation of his CFS occurred within this window. Mr. D'Angiolini's case falters on both aspects.

a) Medically Appropriate Interval between Vaccination and the Onset of Symptoms

Part of a petitioner's burden is to present "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." Bazan, 539 F.3d at 1352. Here, as explained above, medical science has almost no understanding of the etiology of CFS. Therefore, any assertions about the correct timeframe are almost certainly guesses. Since no one knows how CFS develops, how can anyone estimate how long the development takes?

Dr. Shoenfeld's estimates were essentially boundless. In his report, Dr. Shoenfeld stated "in the past, to show a cause and effect of vaccine

⁵⁴ Dr. Vasey accepted Dr. Shoenfeld's suggestion that the hepatitis B vaccine can cause CFS via a process known as molecular mimicry. Tr. 1559-60. Molecular mimicry has been rejected as a basis for finding that the hepatitis B vaccine can cause a disease because the amino acid sequence in the vaccine does not resemble the amino acid sequence in human proteins. See Shapiro, 105 Fed. Cl. at 359.

autoinflammatory reaction, we assumed that the period of time between the vaccine and the reaction has to be somewhere between 3 weeks . . . to 3 months.” Exhibit 87 at 7. Based upon his continued work, including his work on ASIA (discussed below), Dr. Shoenfeld stated that “the period may extend to months and even years, [during when] the adjuvant, loaded into the body, chronically stimulate[s] the immune system.” Id.

At the hearing, Dr. Shoenfeld confirmed his written opinion. When asked during cross-examination about the expected timeframe in which symptoms would be manifest, Dr. Shoenfeld responded “The timeframe is variable. It can cause it in weeks['] time. It can cause it in months['] time. . . . It depends on the number of vaccine[s], . . . and it will depend also on the [recipient's] genetic background.” Tr. 875-76. Later, Dr. Shoenfeld opined that “[t]here is no maximum time.” Tr. 880.⁵⁵

Dr. Shoenfeld's opinion that any amount of time is medically appropriate may reflect different perspectives from law and medicine. See Tr. 882. Controlling precedent requires that petitioners establish the interval between vaccination and the onset of the disease is medically appropriate. Althen, 418 F.3d at 1278. This element prevents a finding that a vaccine caused an adverse event “weeks, months, or years outside of the time in which scientific or epidemiological evidence would expect an onset of harm.” Pafford, 451 F.3d at 1358. As such, when Dr. Shoenfeld has offered an opinion that does not place an outer bound on the appropriate temporal relationship, his opinion has been rejected because “[i]n effect, Dr. Shoenfeld's testimony renders Althen's third prong a nullity.” Hennessey v. Sec'y of Health & Human Servs., 91 Fed. Cl. 126, 142 (2010). In this case, Dr. Shoenfeld's opinion is essentially the same as his opinion in Hennessey and fails to be persuasive for the same reason as explained in Hennessey.

b) Onset of Mr. D'Angiolini's Problems

If Mr. D'Angiolini had established an interval that was medically appropriate, then he would also need to present preponderant evidence that his CFS

⁵⁵ As part of his testimony on direct examination, Dr. Shoenfeld simply stated that Mr. D'Angiolini developed symptoms of chronic fatigue syndrome within a medically appropriate timeframe without describing what the medically appropriate timeframe is. Tr. 812-13.

arose within this timeframe. Shapiro, 101 Fed. Cl. at 542. Once again, Mr. D'Angiolini's case falters.

As described at length above, Mr. D'Angiolini did not prove, by a preponderance of the evidence, that he ever suffered from CFS. Thus, trying to determine when his CFS began is a counterfactual exercise.

It is true, as Dr. Shoenfeld explained, that the diagnosis of CFS is retrospective in that the symptoms of CFS must persist for at least six months. Thus, at least six months will necessarily elapse before the diagnosis can be made. Tr. 875-79. Nevertheless, with the benefit of a retrospective review of the facts and medical records, the expert should be able to opine when the CFS began.

Dr. Shoenfeld, however, had difficulties saying when Mr. D'Angiolini's CFS began. On direct examination, he stated only that the symptoms arose in a medically appropriate timeframe without offering any specific information about when the symptoms arose, other than saying they arose after the vaccinations. Tr. 812-13. At another point in his testimony, Dr. Shoenfeld stated that he recalled that Mr. D'Angiolini's chronic fatigue started to cause a substantial reduction in his life's activities "definitely after the vaccines," and maybe after the second vaccine, specifically. Tr. 961. This testimony is consistent with the opinion Dr. Shoenfeld presented in his May 30, 2011 report that Mr. D'Angiolini's "CFS is due to the [hepatitis B] vaccine given to him on 3/18/97 and 4/[18]/97." Exhibit 95 at 3.

The problem is that the facts of Mr. D'Angiolini's case do not match Dr. Shoenfeld's opinion. After the second vaccination, which was on April 18, 1997, Mr. D'Angiolini did not reduce his activities due to chronic fatigue. For example, he continued to work at two jobs. Exhibit 16 at 263 (Valley Forge); 305-07 (Bachman's Music Store); see also Tr. 595-98. Mr. D'Angiolini's continued employment during this time goes against finding that he suffered the debilitating fatigue that characterizes CFS.⁵⁶ See Tr. 1347-48 (Dr. Lightfoot), 1446-47 (Dr. Shoenfeld).

⁵⁶ Dr. Shoenfeld suggested that (a) Mr. D'Angiolini was fatigued between April 18, 1997, and May 27, 1997, and (b) this fatigue "might be" a manifestation of chronic fatigue syndrome. Tr. 841. Dr. Shoenfeld indicated that he thought that Mr. D'Angiolini was fatigued because Mr. D'Angiolini "didn't complete the assignment of the work." Tr. 841. But, Mr. D'Angiolini's (...continued)

Although Mr. D'Angiolini's initial brief cited the portion of Dr. Shoenfeld's testimony that the CFS possibly began after the second vaccination, Pet'r's Posthr'g Br. at 9, citing Tr. 961; but see id. at 8 (arguing that November 5, 1997 is the "bellwether" for chronic fatigue syndrome), Mr. D'Angiolini's reply brief appears to argue for a different onset. There, Mr. D'Angiolini asserts "[b]oth experts have agreed that November 4, 1997 was a benchmark date with respect to the Chronic Fatigue Syndrome analysis." Pet'r's Posthr'g Reply at 11. Although Mr. D'Angiolini stopped working both his jobs on November 4, 1997, the medical records created close in time to November 4, 1997, do not show that Mr. D'Angiolini was fatigued. He had other problems that interfered with his ability to perform tasks associated with daily living, such as changing his clothes. But, these other problems were not fatigue.

Mr. D'Angiolini's case that he was suffering from chronic fatigue (if not CFS) is stronger if he were to claim that the fatigue began in approximately August 1998. This argument, which Mr. D'Angiolini has not advanced, would have the advantage of being after Mr. D'Angiolini told a doctor that he was running for exercise. Exhibit 15 at 12; see also Tr. 1461 (Dr. Shoenfeld: a person who is running five miles does not have CFS). In addition, Mr. D'Angiolini told at least some doctors in the latter half of 1998 that he was suffering from chronic fatigue. Exhibit 5 at 21 (Dr. Bach, October 10, 1998); exhibit 23 at 32 (Dr. Roman, November 10, 1998); exhibit 22 at 4 (Dr. Norris, November 17, 1998).

An August 1998 onset --- which is assumed for argument's sake --- still presents problems for Mr. D'Angiolini's case. If Mr. D'Angiolini began suffering from chronic fatigue, which was a manifestation of CFS, in August 1998, then approximately ten months would have elapsed after his most recent hepatitis B vaccination, which was on October 24, 1997. An onset of ten months exceeds the amount of time usually presented as a medically appropriate interval. Only Dr. Shoenfeld's boundless timeframe would encompass a ten-month interval.

3. Prong 2 of the Althen Analysis

By now, it should be clear that Mr. D'Angiolini cannot establish "a logical sequence of cause and effect," as set forth in Althen, 418 F.3d at 1278. He has not

performance review for this time was positive. See exhibit 16 at 31 (evaluation covering March 3, 1997 through May 31, 1997).

shown that he suffers from chronic fatigue syndrome. He has not presented a reliable theory explaining how the hepatitis B vaccine can cause CFS. He failed to introduce any legally persuasive evidence of what the appropriate temporal relationship between vaccination and the onset of CFS is. And, he has not proven that his chronic fatigue syndrome, assuming that he has CFS, arose within a timeframe for which it is appropriate to infer causation. Under these circumstances, it is not possible to find that a preponderance of evidence indicates that his claim is “logical.”

This finding is reached despite some contrary evidence from Mr. D’Angiolini’s treating doctors. See Doe v. Sec’y of Health & Human Servs., 601 F.3d 1349, 1358 (Fed. Cir. 2010) (the presence of some contradictory evidence does not preclude a special master’s finding). The views of treating doctors, especially with respect to the second Althen prong are very important. Capizzano, 440 F.3d at 1320. Treating doctors who diagnosed Mr. D’Angiolini as suffering from CFS that was caused by the hepatitis B vaccination are Dr. Buttram, Dr. Waisbren, and Dr. Vasey. See Pet’r’s Prehr’g Br. at 11; Pet’r’s Posthr’g Reply at 6-7.⁵⁷

The Secretary argues that these statements are not persuasive. “With respect to treating physician statements, no treating doctor ascribed causation to the hepatitis B vaccine prior to August, 1999. This is significant because it was around this time that either petitioner or his mother ‘learned that some people believed that the hepatitis B vaccine can cause adverse effects similar to problems experienced by [petitioner].’” Resp’t’s Prehr’g Br. at 18, quoting Findings of Fact at 37. The Secretary points out that “[r]ecords dated after this point are notably absent of any mention of any of petitioner’s pre-vaccination problems, and often reflect that he was in good or excellent health.” Id.

Mr. D’Angiolini does little to rebut this argument. The histories presented to Dr. Buttram, Dr. Waisbren, and Dr. Vasey present a stark contrast between Mr. D’Angiolini’s health before and after vaccination. E.g. exhibit 14 at 23 (Dr. Buttram: “He was in excellent health, working 60 hours / wk until series of

⁵⁷ At other places, Mr. D’Angiolini asserts that doctors diagnosed him with chronic fatigue syndrome. But, these doctors’ diagnoses are not the same as a statement that the hepatitis B vaccine caused the CFS. Thus, although they have been considered, they are not discussed at length.

hepatitis B vaccinations March, April, Oct. 1997.”); exhibit 21 at 9 (Dr. Waisbren: “This 32-year-old male was in excellent health in March of 1997 when he received his first hepatitis B vaccination. Past history up to that time revealed only seasonal allergies and some allergy to yeast.”); exhibit 133 at 19 (Dr. Vasey: “After the first injection he developed promptly some headaches and flu-like symptoms.”).

As determined in the Findings of Fact, Mr. D’Angiolini’s history from January through November 1997, was complicated. He functioned well enough to work two jobs. Yet, he was also experiencing a worsening of his long-standing OCD requiring prescription medications. And, when Mr. D’Angiolini had a precipitous decline in November 1997, the contemporaneously created records do not say that he experienced fatigue. Consequently, the histories provided to Doctors Buttram, Waisbren and Vasey are not a sound basis for deriving a persuasive medical opinion. See Burns, 3 F.3d at 417.

E. Synopsis of CFS

Mr. D’Angiolini is not entitled to compensation on his claim that the hepatitis B vaccination caused him to suffer chronic fatigue syndrome. He has not established that he suffered from chronic fatigue syndrome. He also has not established that there is proximate causal relationship between the hepatitis B vaccine and chronic fatigue syndrome.

VII. Lupus

Lupus is an autoimmune disease that affects many organs. Tr. 1128. The American College of Rheumatologists issued a set of criteria for classifying lupus in 1982. Tr. 896. Because the lead author of the article announcing these criteria was Eng Tan, the criteria are sometimes known as the Tan criteria. Exhibit T (Eng M. Tan et al., The 1982 Revised Criteria for the Classification of Systemic Lupus Erythematosus, 25 Arthritis Rheumatism 11 (1982)). Similar to the process for developing criteria for chronic fatigue syndrome, the Tan criteria were slightly modified in 1997. Exhibit L (1997 Update of the 1982 American College of

Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus (1997)).⁵⁸

As explained earlier, see section II, Mr. D'Angiolini bears the burden of establishing that he suffers from lupus. Lombardi, 656 F.3d at 1352.⁵⁹ Section A explores this topic and concludes that Mr. D'Angiolini's claim was not persuasive. This finding is the basis for the explanation, in section B, for why an analysis of the Althen prongs is not needed.

A. Has Mr. D'Angiolini Established by Preponderant Evidence that He Suffers from Lupus?

The evidence relevant to Mr. D'Angiolini's claim that he suffers from lupus comes from a variety of sources, reflecting the extensive medical attention given to him. The primary source is Dr. Vasey, a rheumatologist who has treated him since 2000. Dr. Vasey stated that Mr. D'Angiolini does not have lupus. See section 1. Mr. D'Angiolini emphasizes the views of other treating doctors, including Dr. Bray, the providers from the Cleveland Clinic, and Dr. Pretorius. See section 2. The symptoms recounted by the treating doctors and the signs found by the treating doctors are the basis for opinions provided by the doctors specially retained for this litigation, Dr. Shoenfeld and Dr. Lightfoot. See section 3. Collectively, all this information is analyzed to see whether the evidence supports a finding that Mr. D'Angiolini fulfills any of the lupus criteria. See section 4.

⁵⁸ In general, the 1982 Tan criteria describe the particular signs or symptoms more extensively. Thus, when there is no difference between the 1982 criteria and the 1997 criteria, this decision cites to the 1982 version.

⁵⁹ Coincidentally, the factual setting in Lombardi resembles the factual setting in this case. In Lombardi, Dr. Shoenfeld opined that the petitioner suffered from lupus. The (undersigned) special master found his opinion was not persuasive because, in part, none of her treating doctors diagnosed her with lupus. Doe 60 v. Sec'y of Health & Human Servs., No. redacted, 2010 WL 1506010 (Fed. Cl. Mar. 26, 2010). This factual finding was upheld on appeal as not being arbitrary or capricious at both the Court of Federal Claims, Doe 60 v. Sec'y of Health & Human Servs., 94 Fed. Cl. 597, 618-19 (2010), and the Federal Circuit, Lombardi, 656 F.3d at 1354-55.

1. Treating Doctors – Dr. Vasey

When the question is what diagnosis best captures the disease affecting the petitioner, a treating doctor stands in a knowledgeable position. The treating doctor can see, touch, and listen to the patient. This first-hand information may provide insights to the patient's problems that are unavailable to a doctor who is reviewing only medical records. Hence, the views of the treating doctors are entitled to careful consideration when it comes to diagnosis. See Capizzano, 440 F.3d at 1326.

While potentially influential, the opinions of treating doctors are not always controlling. The Vaccine Act specifies that special masters are not bound by the diagnosis of a treating doctor. See 42 U.S.C. § 300aa–13(b)(1).

This case illustrates why a treating doctor's diagnosis cannot bind a special master. Here, as discussed below, the treating doctors reach opposite conclusions. Some doctors have indicated (or suggested) that Mr. D'Angiolini suffers from lupus. Another doctor, Dr. Vasey, has stated that Mr. D'Angiolini does not suffer from lupus. It seems quite unlikely that both positions can be correct. When the evidence is in conflict, the special master may determine what evidence is more persuasive. Broekelschen, 618 F.3d at 1346-49; see also Whitecotton v. Sec'y of Health & Human Servs., 81 F.3d 1099, 1108 (Fed. Cir. 1996).

Dr. Vasey's opinion regarding diagnosis is more persuasive. Three reasons support the strength of Dr. Vasey in this regard. First, Dr. Vasey is a rheumatologist. He regularly treats people with lupus. Tr. 1568. Second, Dr. Vasey saw Mr. D'Angiolini over an extended duration, more than a decade. The combination of these two factors means that Dr. Vasey has both the ability to diagnose lupus and the opportunity to do so. As explained below, the treating doctors who support the lupus diagnosis seem to be comparatively weaker. Finally (but less importantly), Dr. Vasey testified about his opinion. Dr. Vasey's willingness to answer questions about his diagnosis adds a small measure of confidence to it.

Dr. Vasey's experience is an important factor in weighing his opinion. He is board certified in rheumatology. Tr. 1508. People with lupus frequently seek treatment from rheumatologists. Tr. 1129. Dr. Vasey has seen more than 100 patients with lupus in his career. Tr. 1568. Many of these encounters occurred when Dr. Vasey worked at a clinic in Detroit serving an urban African-American

population, which he identified as having an increased risk for lupus. Exhibit 86; Tr. 1568.

Another valuable factor is Dr. Vasey's experience with Mr. D'Angiolini in particular. Dr. Vasey first saw Mr. D'Angiolini upon a referral from Mr. D'Angiolini's mother, for whom Dr. Vasey had cared. The first appointment between Dr. Vasey and Mr. D'Angiolini was on September 29, 2000. At this visit, Mr. D'Angiolini gave Dr. Vasey a history, although Mr. D'Angiolini did not provide any medical records. Tr. 1535. After this initial consultation, Dr. Vasey wrote a letter to the judge presiding over Mr. D'Angiolini's claim for workers' compensation benefits. Exhibit 133 at 23.

Dr. Vasey described his findings in a series of medical records, which were submitted as exhibit 133.⁶⁰ These records show that approximately one year passed between Mr. D'Angiolini's initial appointment, which was on September 29, 2000, and his second appointment, which was on September 19, 2001. See Tr. 1513. The third appointment occurred on July 30, 2003. Tr. 1514.

Following the third appointment, Dr. Vasey generally saw Mr. D'Angiolini approximately two times per year from 2003 to 2012. Dr. Vasey's most recent appointment was on June 6, 2012. Tr. 1525. Mr. D'Angiolini's attorney asked Dr. Vasey about these visits. Tr. 1514-25. Dr. Vasey did not include lupus as a diagnosis on any of these records.

In the context of presenting an opinion for this litigation, Dr. Vasey was asked to consider whether Mr. D'Angiolini had lupus. See order, filed June 7, 2011. Dr. Vasey's response was "I agree with Dr. Lightfoot that at no time when I cared for him did he meet the criteria for lupus." Exhibit 96 at 1.

Dr. Vasey maintained this opinion throughout his testimony. He explained:

I would say that [during] the evolution over the 13 years I've followed him, there was no overwhelming evidence of lupus. But his neuro-mental dysfunction, his cardiac dysfunction, all those are

⁶⁰ Dr. Vasey's records appear in other places in the record, too. But, exhibit 133 is the most complete source.

typically seen in rheumatic disease patients such as lupus patients, which is [an] archetypical immune disorder.

So while he doesn't meet the criteria for lupus in my opinion, there's clear evidence from the record that he has immune dysfunction syndrome, whatever you call it.

Tr. 1548-49.

When Dr. Vasey was asked whether Mr. D'Angiolini suffered from lupus when Dr. Vasey first saw him on September 29, 2000, Dr. Vasey again denied the lupus diagnosis. Dr. Vasey stated:

And I know that there's been a lot of discussion, mostly with others, about whether or not he had lupus. I certainly don't think he did. The times I saw him, which it was somewhere near middly, about every six months or so. Is it possible to have lupus in between when I saw him? Certainly that's possible. But I didn't get a story of a malar rash or pleuritis, parotitis, polyarthritis. Even his ANA, the few I saw from outside physicians were negative. So I mean the possibility of lupus never – to be honest, never really crossed [my] mind with any degree of concern.

Tr. 1574.

Dr. Vasey's testimony that when he was treating Mr. D'Angiolini, the possibility that Mr. D'Angiolini suffered from lupus was such a remote possibility that it "never . . . crossed [his] mind" is strong evidence that Mr. D'Angiolini did not suffer from lupus. It gains additional strength because when Dr. Vasey was asked to consider whether Mr. D'Angiolini suffered from lupus, Dr. Vasey confirmed that he did not.

Mr. D'Angiolini offers no argument to explain why Dr. Vasey's opinion that he does not suffer from lupus is wrong. Mr. D'Angiolini's briefs do not discuss Dr. Vasey's non-diagnosis at all. See Pet'r's Br., filed Jan. 5, 2012; see also Pet'r's Suppl. Br., filed June 4, 2012; Pet'r's Postthr'g Br., filed May 21, 2013; Pet'r's Reply Br., filed Aug. 20, 2013. Instead, Mr. D'Angiolini relies upon the statement of other treating doctors.

2. Other Treating Doctors

Although Mr. D'Angiolini's post-hearing briefs do not explicitly rely upon medical records from a treating doctor suggesting that Mr. D'Angiolini suffered from lupus, Mr. D'Angiolini referenced these documents during the hearing. Thus, the consideration on this issue necessarily entails review of these sources.

a) Dr. Bray

The extent of Dr. Bray's treatment is set out exhaustively above. See section III.C.1 above. A brief summary is that in November 1997, after seeing Mr. D'Angiolini, Dr. Bray diagnosed him as having "severe depression" and other psychiatric illnesses. Exhibit 61. In 1999, after learning about the Vaccine Program, Dr. Bray referred Mr. D'Angiolini to a doctor, apparently either Dr. Buttram or Dr. Waisbren. Exhibit 16 at 229.

Dr. Buttram and Dr. Waisbren reached similar conclusions. Both linked the hepatitis B vaccine to Mr. D'Angiolini's decline in health. Exhibit 17 at 125 (Nov. 1, 1999 letter from Dr. Buttram), 39 (case report from Dr. Waisbren). Dr. Buttram stated that Mr. D'Angiolini suffered from "chronic fatigue and myocarditis." Id. at 125. Dr. Waisbren identified "post vaccinal encephalomyelitis and generalized autoimmunity." Id. at 39.

In his February 22, 2000 letter, Dr. Bray continued to say that Mr. D'Angiolini suffered from depression, although Dr. Bray characterized his depression as secondary to a chronic illness. Dr. Bray added other diagnoses, including "systemic autoimmune disease" and "post encephalomyelitis." Exhibit 17 at 109-10. Later, on May 9, 2002, Dr. Bray added one more diagnosis, SLE. Exhibit 131 at 3.

Thus, Dr. Bray's May 9, 2002 letter constitutes some evidence supporting an assertion that Mr. D'Angiolini suffered from SLE. The challenge comes from trying to weigh this evidence especially in light of the fact that another one of Mr. D'Angiolini's treating doctors, Dr. Vasey, did not see evidence of SLE even though Dr. Vasey's treatment occurred in the same time. Because it appears that the basis for Dr. Bray's conclusion overlaps with Dr. Shoenfeld's rationale, a more extensive discussion of Mr. D'Angiolini's signs and symptoms that arguably support the lupus diagnosis is deferred to section VII.A.4 below.

b) Cleveland Clinic Doctors, including Doctors Hanson and Galatro

The context for Mr. D'Angiolini's visits with doctors from the Cleveland Clinic is recounted in section III.C.6, above. The strongest evidence regarding lupus is Dr. Hanson's statement that "I rather agree with Dr. Galatro that this is an autoimmune disorder which falls presum[ably] into the lupus category." Exhibit 37 at 25. In addition on June 22, 2005, Dr. Galatro's impression was "[m]ild cardiomyopathy" and "SLE." Dr. Galatro prescribed medication for Mr. D'Angiolini's cardiomyopathy but did not recommend any particular treatment or study specifically for SLE. *Id.* at 20.

c) Dr. Pretorius – SPECT scan

The SPECT scan results from Dr. Pretorius's June 2003 evaluation of Mr. D'Angiolini are discussed in section III.C.5, above. In his assessment of these results, Dr. Pretorius suggests "[l]upus-like cerebritis (evidenced also by positive double-stranded DNA antibodies) related to repeated antigen (vaccine) exposure is most likely in a patient with multiple documented allergies." Exhibit 40 at 2.

3. Specially Retained Expert Witnesses

a) Dr. Shoenfeld

In his expert report, Dr. Shoenfeld opined that Mr. D'Angiolini suffered from SLE. Exhibit 87 at 11. He supported his opinion by relying upon four features: a decrease in the amount of complement, the presence of anti-DNA antibodies, a problem in Mr. D'Angiolini's brain, and a problem in Mr. D'Angiolini's heart. Exhibit 87 at 11. Dr. Shoenfeld based his opinion, in part, on the laboratory studies that Dr. Buttram and Dr. Waisbren ordered at the end of 1999. *Id.*; *see also* Tr. 743-44. In his testimony, Dr. Shoenfeld specified that the central nervous system involvement was "sleepiness and cognitive impairment and so forth" and the heart aspect was "cardiomyopathy." Tr. 743.⁶¹ Mr. D'Angiolini puts forward these criteria in his posthearing brief. Pet'r's Posthr'g Br. at 21-22.

⁶¹ Later, Dr. Shoenfeld added muscle pain and malar rash. Tr. 885.

b) Dr. Lightfoot

Dr. Lightfoot's opinion was that Mr. D'Angiolini did not suffer from SLE. Dr. Lightfoot expressed his disagreement with Dr. Shoenfeld's contrary opinion thusly:

He [Dr. Shoenfeld] states that petitioner has "clear cut diagnosed SLE," which is simply a misstatement of fact. SLE is not the diagnosis of any other clinician involved in petitioner's care. . . Except for his transient and very borderline anti-DNA, . . . he really meets none of the criteria for SLE, and four are required to establish an unequivocal diagnosis.

Exhibit A at 16.

c) Assessment

Dr. Lightfoot's opinion that Mr. D'Angiolini did not suffer from lupus was more persuasive than Dr. Shoenfeld's opinion that he did. As discussed below, Dr. Lightfoot's opinion closely tracks the diagnostic criteria. Dr. Shoenfeld, on the other hand, expanded the criteria beyond what the criteria specify.

In accord with the approach taken in Doe 60 / Lombardi, the diagnostic criteria are reviewed. For each criterion, the evidence supporting a positive finding is reviewed.

4. Diagnostic Criteria⁶²

a) Immunologic Disorder -- Complement

Complement refers to a series of many proteins located in the blood. Dorland's at 393. Complement is part of the immune system. Tr. 742. When

⁶² The Tan criteria are attached hereto as "Appendix B."

tested by Dr. Waisbren in 1999, Mr. D'Angiolini's complement levels were low. Exhibit 3 at 11.⁶³

Dr. Shoenfeld placed the low complement within the "immunologic disorder" criterion of the 1982 criteria for diagnosing lupus. Dr. Shoenfeld frequently brought out the low complement as supporting the SLE diagnosis. Tr. 743, 749, 810, 838, 883, 885. In his initial post-hearing brief, Mr. D'Angiolini discusses the low complement levels. Pet'r's Posthr'g Br. at 21-22. But, Dr. Shoenfeld contradicted his own opinion. Dr. Shoenfeld acknowledged that low complement does not fit in the revised criteria. Tr. 895.

According to Dr. Lightfoot, low complement is not part of the immunological abnormalities that are part of the criteria for lupus. Tr. 1130-31, 1145. He explained that studies have shown that in people with SLE, complement levels float "in and out of normal range." Tr. 1146-47.

Therefore, Dr. Shoenfeld and Dr. Lightfoot agree that the most recent criteria for diagnosing SLE do not use low complement levels as a factor supporting diagnosis. While Dr. Shoenfeld may be correct that low complement would affect the determination using the previous criteria, Dr. Shoenfeld did not explain why the out-of-date criteria should be used. Furthermore, in his reply brief, Mr. D'Angiolini no longer claimed to meet this criterion because of the low complement. Rather, Mr. D'Angiolini argued the positive result on an anti-DNA test fulfilled this criterion. Pet'r's Reply Br. at 19.

b) Immunologic Disorder – anti-DNA antibodies

In December 1999, Dr. Waisbren tested Mr. D'Angiolini for native DNA antibodies. Exhibit 20 at 34. The result was 59 IU/ML, which was positive. (Positive values started when the result exceeded 55 IU/ML.).⁶⁴ Dr. Shoenfeld relied upon this sign for the SLE diagnosis. Tr. 742, 810, 884. He stated that he "ha[s] to emphasize that the presence of anti-DNA antibodies per se do not indicate

⁶³ Dr. Lightfoot questioned the validity of the result for low complement. See Tr. 1144, 1247, 1490-93; exhibit A at 13. But, Dr. Shoenfeld disagreed. See Tr. 1436-38. However, it is not necessary to address this level of detail for reasons explained in the text.

⁶⁴ The current edition of Mosby's indicates that values less than 70 international units / mL are negative. Mosby's at 80.

by itself that it's lupus or another autoimmune rheumatic disease." Tr. 742; accord Tr. 883.

Later testing was not consistent. Another test Dr. Waisbren ordered in July 2001, produced a negative result, meaning that Mr. D'Angiolini had less than 25 IU/ML. Exhibit 20 at 45. Similarly, testing from the Cleveland Clinic from September 2004, was also negative. Exhibit 37 at 3, 10. It is unlikely that the amount of antibodies produced by Mr. D'Angiolini fluctuated. Tr. 1111-12; but see Tr. 1488-89.

Dr. Lightfoot explained that the more likely explanation for the slightly positive test in December 1999 concerns some errors (or artifact) in testing and the need to differentiate between double-stranded DNA and single-stranded DNA. Tr. 1109-11; see also Tr. 1307, 1491; exhibit A at 12 (describing difficulties in testing for anti-DNA antibodies); but see Tr. 1499-500 (Dr. Lightfoot stating that his testimony about an artifact in testing is speculation but "based on considerable experience in the area"). Dr. Vasey concurred that testing for single-stranded DNA has been "discredited as being likely non-specific." Tr. 1568.

c) Serositis

The basic definition of "serositis" is "inflammation of a serous membrane." Dorland's at 1698. A serous membrane, in turn, is one that pertains to serum. Id. at 1699. For purposes of SLE diagnosis, serositis is defined as:

Pleuritis --convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion

OR

Pericarditis---documented by ECG or rub or evidence of pericardial effusion

Exhibit T (Tan) at 1274. "Pericarditis" means inflammation in the fibroserous sac surrounding the heart. Dorland's at 1411-12.

In Dr. Shoenfeld's opinion, Mr. D'Angiolini met the serositis criterion by having cardiomyopathy. The term "cardiomyopathy" means the person has "some kind of pathology in [his or her] heart." Tr. 733; accord Tr. 1142-43; Dorland's at 294. Dr. Shoenfeld listed Mr. D'Angiolini's heart involvement as supporting the SLE diagnosis. Exhibit 87 at 6, 11.

Dr. Lightfoot maintained that Mr. D'Angiolini did not suffer from pleuritis or pericarditis. Exhibit A at 16.

Mr. D'Angiolini's pretrial submission said "serositis – none." Pet'r's Suppl. Br., tab C, at 2. It is not clear whether Mr. D'Angiolini intended to disagree with his expert's view that cardiomyopathy qualified as part of the lupus criteria.

Regardless of the position taken in Mr. D'Angiolini's brief, Dr. Shoenfeld testified that Mr. D'Angiolini's cardiomyopathy satisfied one of the lupus criteria. See Tr. 733-35, 898-99. Dr. Lightfoot disagreed. According to Dr. Lightfoot, cardiomyopathy differs from pericarditis. Pericarditis is "inflammation of the lining around the heart." Tr. 1142; accord Dorland's at 1411-12. Mr. D'Angiolini's cardiomyopathy does not fulfill the criteria for lupus. Tr. 1130-31, 1142-43.

Given that the diagnostic criteria refers to "pericarditis," the lining of the heart muscle and not to the heart generally, it appears that Dr. Shoenfeld's interpretation broadens the criteria. Dr. Vasey shared this view. Dr. Vasey stated that cardiomyopathy does not qualify as pericarditis because they are "different." Tr. 1575.

Consequently, Mr. D'Angiolini does not satisfy the serositis criterion.⁶⁵

d) Neurologic Disorder

With exceptions not pertinent here, the diagnostic criteria for a neurologic disorder in lupus are seizures or psychosis. Exhibit T (Tan) at 1274. "Psychosis," in turn generally refers to "mental disorders in which mental functioning is so

⁶⁵ The foregoing analysis presumes that the assertion that Mr. D'Angiolini suffered from cardiomyopathy is correct. This assertion appears based upon an October 20, 1998 echocardiogram, which showed that Mr. D'Angiolini's heart's ability to pump blood was "at most mildly to moderately depressed." However, this echocardiogram was a "technically difficult study." Exhibit 6 at 7.

When Mr. D'Angiolini had another echocardiogram at the Cleveland Clinic in 2004, his ejection fraction was 45 percent. Exhibit 37 at 18-20. These results prompted Dr. Lightfoot to testify that he was not sure whether Mr. D'Angiolini actually had a cardiomyopathy. Tr. 1140-41.

Resolving whether Mr. D'Angiolini had a cardiomyopathy is not necessary because a preponderance of the evidence, including Dr. Vasey's testimony, establishes that a general cardiomyopathy does not satisfy the lupus criteria.

impaired that it interferes grossly with the patient's capacity to meet the ordinary demands of life." Dorland's at 1550.

By a conventional definition of "psychosis," Mr. D'Angiolini did not have this problem. Between 1996 and 2000, Mr. D'Angiolini was seeing a psychiatrist regularly. Dr. Middleman did not diagnose him as suffering from psychosis. See exhibit 24. Thomas Sacchetti, a neuropsychologist, examined Mr. D'Angiolini in September 2004, and did not diagnose a psychosis. Exhibit 48. One of Mr. D'Angiolini's doctors from the Cleveland Clinic, Dr. Hanson, reviewed Dr. Sacchetti's report and stated "it did not document any evidence of psychosis [or] a psychiatric disorder." Exhibit 37 at 25. Consequently, Mr. D'Angiolini does not fit the usual definition of "psychosis."

However, Dr. Shoenfeld does not have the common understanding of "psychosis." To Dr. Shoenfeld, a cognitive impairment is sufficient to be a psychosis. Tr. 897 (Dr. Shoenfeld "when you have cognitive impairment, it may be the equivalent" of psychosis); see also Tr. 743 (Dr. Shoenfeld finding evidence that Mr. D'Angiolini's central nervous is involved because of his "sleepiness and cognitive impairment and so forth").

Mr. D'Angiolini has not established that "psychosis," as used in the Tan criteria, is so broad that it encompasses his cognitive impairments. Dr. Shoenfeld's stretching of the criteria is not supported by anything beyond Dr. Shoenfeld's own statements.

Mr. D'Angiolini makes two other attempts to fall within the "psychosis" category. First, he maintains that a SPECT scan conducted by Dr. Pretorius in November 1998, shows changes in his brain tantamount to psychosis. See Pet'r's Reply Br. at 19. It is true that Dr. Pretorius interpreted the SPECT scan as showing "Lupus-like cerebritis," exhibit 40 at 2, and Dr. Shoenfeld deferred to this interpretation. Tr. 1035-49. While the SPECT scan may have shown inflammation in Mr. D'Angiolini's brain, inflammation is not the same as psychosis. Moreover, the relative newness of using SPECT scans in diagnosing lupus raises legitimate questions about the accuracy of labeling a particular pattern as consistent with lupus. See Tr. 1136-41, 1251-58, 1325.

Second, Mr. D'Angiolini cites to other reports of "neurological maladies." Pet'r's Reply Br. at 19. But, the various neurologic problems reported by some of

Mr. D'Angiolini's treating doctors (for example, headaches) do not fulfill the Tan criteria for lupus.⁶⁶

In short, there is no persuasive evidence that Mr. D'Angiolini had either seizures or psychosis, which are the two alternative ways of fulfilling this criterion.

e) Arthritis

The lupus criteria include "arthritis" which is defined as "Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion." Exhibit T (Tan) at 1274. Evidence that Mr. D'Angiolini met this criterion arguably comes from two different sources, Dr. Shoenfeld and his medical records.

In Dr. Shoenfeld's report, he identified "muscles involvement[]" as supporting the lupus diagnosis. Exhibit 87 at 11. Dr. Shoenfeld did not specifically list joint problems in this portion of his report, although Dr. Shoenfeld mentioned joints in other portions of the report. E.g. id. at 6, 12. When Dr. Shoenfeld testified, he linked Mr. D'Angiolini's muscle pain to joint pain. See Tr. 883, 897-98, 1438.⁶⁷ Dr. Shoenfeld went so far as to say "the pains in the muscle, the muscle pain, the myalgia may be the first symptom of his SLE." Tr. 885.

Dr. Lightfoot's response to myalgia was both succinct and persuasive. When asked whether myalgia is evidence of lupus, Dr. Lightfoot said "[m]yalgia is not." Tr. 1143.

Again, Dr. Lightfoot's testimony that myalgia is not a feature of SLE is in accord with the Tan article. Exhibit T (Tan) at 1274. Thus, it is easy to reject Dr.

⁶⁶ Mr. D'Angiolini mischaracterizes the Secretary's position. Mr. D'Angiolini states that under the neurologic disorder, "Respondent alleges that Joseph must exhibit a seizure to satisfy this criteri[on]." Pet'r's Reply Br. at 18. Mr. D'Angiolini's attempt to restrict the Secretary's argument to just seizures is not correct. The Secretary actually argued "a) seizures . . . OR b) psychosis." Resp't's Postthr'g Br. at 33, quoting exhibit T (Tan) at 1274.

⁶⁷ Dr. Shoenfeld was never directly asked to explain which of the 11 criteria muscle pain fits. Muscle pain fits, if at all, only with arthritis.

Shoenfeld's opinion, reflected in his written report, that Mr. D'Angiolini's muscle pain is part of SLE.⁶⁸

In his oral testimony, Dr. Shoenfeld also discussed Mr. D'Angiolini's arthralgia as meeting the definition of arthritis. In a medical dictionary, "arthralgia" means "pain in a joint," while "arthritis" means "inflammation of a joint." Dorland's at 150. In Dr. Shoenfeld's vernacular, "[a]rthralgia is arthritis that you don't see." Tr. 898. Upon further questioning, Dr. Shoenfeld confirmed that, to him, arthralgia and arthritis are the same. Id. Dr. Shoenfeld equates Mr. D'Angiolini's reports of joint pain with inflammation in the joints. Tr. 1439.

Dr. Lightfoot did not accept Dr. Shoenfeld's blurring of arthritis and arthralgia. Tr. 1143. Dr. Lightfoot's opinion stays within the criteria. The criteria use the term "arthritis," not "arthralgia." Consequently, Dr. Shoenfeld's opinion is not persuasive.

In addition to the testimony from Dr. Shoenfeld, Mr. D'Angiolini relies upon notations from his treating doctors. See Pet'r's Suppl. Br., tab C at 2, Pet'r's Reply Br. at 18.⁶⁹ Dr. Buttram in October 1999 included "joint pains [that] come + go." Exhibit 36 at 18. However, on Dr. Buttram's typed checklist of past and present symptoms, Mr. D'Angiolini did not check either rheumatoid arthritis or degenerative arthritis. See id. at 27.

The strongest evidence that Mr. D'Angiolini suffered from arthritis as defined in the criteria is the May 9, 2002 letter from Dr. Bray seeking disability benefits. The provenance of this letter is set forth above. Dr. Bray reported that he saw Mr. D'Angiolini on May 9, 2002, and conducted a physical examination, revealing "[t]enderness and swelling of the joints of the ankles, knees, and elbows." Exhibit 131 at 4. Dr. Lightfoot acknowledged that joint tenderness meets the definition. Tr. 1424-25.

⁶⁸ Mr. D'Angiolini did not cite muscle problems as evidence for SLE. Pet'r's Postthr'g Br. at 21-22; Pet'r's Reply Br. at 17-20.

⁶⁹ Dr. Shoenfeld did not rely upon the reports of these doctors in his testimony.

Years later, Dr. Vasey found that Mr. D'Angiolini did not have joint tenderness. Exhibit 133 at 5 (May 9, 2007), 6 (October 24, 2007), 1 (January 26, 2009).

To recap, in Dr. Shoenfeld's written report, he identified five features of Mr. D'Angiolini in support of the lupus diagnosis. Three (low complement, neurologic involvement, and heart) are definitely out. For the other two (arthritis and anti-DNA antibodies), there is at least a modicum of evidence. However, it is distressing that Dr. Shoenfeld offered opinions that are based upon stretched interpretations of the diagnostic criteria or stretched interpretations of medical records.

In addition to the five features discussed in Dr. Shoenfeld's report, Mr. D'Angiolini asserted that he met other Tan criteria including malar rash, oral ulcers, renal disorder and photosensitivity. The evidence presented for these additional criteria is discussed below.

f) Malar Rash

A rash along the nose, known as a malar rash, is characteristic for lupus. Exhibit T (Tan) at 1274; Tr. 884.

Evidence about Mr. D'Angiolini having a malar rash appears in only three places. See Pet'r's Suppl. Br., tab C, at 2. Two of them are letters from Dr. Bray. Exhibit 17 at 110; exhibit 131 at 4. Dr. Lightfoot acknowledged that Dr. Bray listed malar rash in his letters. Tr. 1245.

The third source is Dr. Buttram. The March 21, 2001 handwritten notes from Dr. Buttram in the history of present illness section state: "He has been running intermittent fever --- running rashes on bridge of nose --- temporal arteritis-type headaches." Exhibit 36 at 1. This report, which appears to come from Mr. D'Angiolini as a historian, is confirmed by Dr. Buttram's physical examination in which skin is associated with "lupus-type facial rash." Exhibit 36 at 2.

The problem, however, is that other doctors do not report similarly. See Tr. 1415, 1428; but see Tr. 1443 (Dr. Shoenfeld: "only one physician noticed malar rash. It doesn't mean it doesn't exist. If the physician saw it, it does").

Dr. Vasey testified that he "didn't personally see a butterfly rash." Tr. 1548; accord Tr. 1572 ("For lupus, I didn't see the malar rash"), 1574 ("I didn't get a

story of a malar rash”). A malar rash is significant because if a patient had a malar rash and a positive test for antinuclear antibodies, then Dr. Vasey would have prescribed a medication. Tr. 1577.

Dr. Bray’s and Dr. Buttram’s reports of a malar rash constitute some evidence that Mr. D’Angiolini did have this rash at some point. It seems unlikely that a doctor would affirmatively state that he saw something if he actually did not see it. Cf. Cucuras v. Sec’y of Health & Human Servs., 993 F.2d 1525, 1528 (Fed. Cir. 1993). However, the lack of reports from other doctors and Dr. Vasey’s testimony that he did not see a malar rash when he saw Mr. D’Angiolini for more than decade make finding a persistent malar rash difficult.

g) Oral Ulcers

The Tan criteria define oral ulcers as “[o]ral or nasopharyngeal ulceration, usually painless, observed by a physician.” Exhibit T (Tan) at 1274. For this factor, in his prehearing submission, Mr. D’Angiolini relied upon Dr. Bray’s letters. Pet’r’s Suppl. Br., tab C, at 2.

Although Mr. D’Angiolini appeared not to be putting oral ulcers forward as part of his lupus diagnosis, the Secretary addressed this topic. She maintained that Mr. D’Angiolini did not meet this criterion because on “multiple occasions,” Mr. D’Angiolini denied having them. Resp’t’s Postthr’g Br. at 31.

On November 17, 1998, Mr. D’Angiolini visited Penn Center for Primary Care, where, it appears, Dr. Anne Norris saw him. Under physical examination, Dr. Norris wrote “[negative] oral lesions.” Exhibit 22 at 3. Dr. Norris made an identical remark on January 19, 1999. Id. at 2. These two reports provide some confirmation that on “multiple occasions” (here, two occasions), Mr. D’Angiolini did not have oral ulcers.⁷⁰

Other than Dr. Bray’s letters, the next report of oral ulcers comes on April 26, 2006. Then, Dr. Vasey reported seeing oral ulcers. Exhibit 133 at 9; Tr. 1518. However, Dr. Vasey did not see mouth ulcers in January 2009, after Mr.

⁷⁰ Another record from around this time comes from Dr. Buttram, whom Mr. D’Angiolini saw in October 1999. Dr. Buttram’s checklist of problems includes “aphthous ulcers,” but Mr. D’Angiolini did not check this box. Exhibit 36 at 15, 26. However, Mr. D’Angiolini may not have understood that aphthous ulcers are oral ulcers.

D'Angiolini included them on his history. Exhibit 133 at 1; Tr. 1578. Dr. Vasey did not find oral ulcers in October 2007. Exhibit 133 at 6.

Overall, the evidence relating to oral ulcers is sparse at best. Neither Dr. Shoenfeld nor Dr. Lightfoot testified about ulcers at all. Dr. Norris's two records support a finding that in 1998 and 1999, he was not having oral ulcers. Dr. Bray's letters, although less reliable for reasons explained above, provide some modicum of support that Mr. D'Angiolini had oral ulcers in February 2000. Exhibit 17 at 110. Mr. D'Angiolini has not identified other treating doctors who reported similar complaints or who made a similar finding.

Dr. Vasey said oral ulcers "can come and go." Tr. 1578. This statement is in accord with common experience. Mr. D'Angiolini has not met his burden of establishing that three reports of oral ulcers across more than a decade of medical records are sufficient to fulfill the lupus criterion.

h) Renal Disorder

Another category of the lupus criteria is renal disorder. This is defined as "a) Persistent proteinuria greater than 0.5 grams per day or greater than 3+ if quantitation not performed OR b) Cellular casts -- may be red cell, hemoglobin, granular, tubular, or mixed." Exhibit T (Tan) at 1274.

For this aspect, Mr. D'Angiolini cites Dr. Bray. Pet'r's Suppl. Br., tab C at 2, citing exhibit 17 at 110. Mr. D'Angiolini did not cite to an underlying lab report.

Although Dr. Bray's report appears multiple times in the record because it is included in the files of other doctors, Mr. D'Angiolini has not identified any other doctors who stated that he had protein in his urine. Because this criterion requires "persistent proteinuria," it appears that an isolated instance of proteinuria does not satisfy the criteria. Dr. Lightfoot maintained that the evidence of protein in Mr. D'Angiolini's urine was not specific to the certain type of nephritis attributable to SLE. Tr. 1305.

i) **Photosensitivity**

The final category put forward by Mr. D'Angiolini is photosensitivity.⁷¹ Doctors Bach and Bray each made a single reference to Mr. D'Angiolini experiencing "light sensitivity." Exhibit 5 at 26; exhibit 131 at 4. During an October 10, 1998 visit to Dr. Bach, Mr. D'Angiolini reported "light sensitivity." Exhibit 5 at 26. Some years following this single report, Dr. Bray listed "light sensitivity" as one of Mr. D'Angiolini's subjective symptoms in his May 9, 2002, letter. Exhibit 131 at 4. Dr. Shoenfeld stated that he did not believe Mr. D'Angiolini had photosensitivity but later included it as part of Mr. D'Angiolini's SLE symptoms after Dr. Bray's reference was brought to his attention. Tr. 890, 1443.

Again, Dr. Shoenfeld seems to stretch a Tan diagnostic criterion. Photosensitivity is defined by Tan as a: "[s]kin rash as a result of unusual reaction to sunlight." Exhibit T (Tan) at 1274. Mr. D'Angiolini's medical records do not indicate any such rash existed. Two distant notations of "light sensitivity," without further detail as to the type or severity of this sensitivity, do not establish that Mr. D'Angiolini suffered from "photosensitivity" as defined by the Tan criteria.

j) **Antinuclear Antibody**

Although Mr. D'Angiolini did not rely upon antinuclear antibodies, the lupus criteria include the presence of antinuclear antibodies. Exhibit T (Tan) at 1274. Dr. Lightfoot stated "[n]inety-five to 97 percent of patients with lupus have a positive ANA." Tr. 1100. As a separate criterion, ANA is "highly sensitive for SLE." Tr. 1132. Dr. Shoenfeld did not counter these assertions in his rebuttal. A commonly used reference book states: "[b]ecause almost all patients with SLE develop autoantibodies, a negative ANA test excludes the diagnosis." Mosby's at 90.

Mr. D'Angiolini's ANA tests have been normal. See Tr. 1100, 1549. Thus, this factor weighs heavily against finding Mr. D'Angiolini suffers from lupus.

⁷¹ Mr. D'Angiolini did not claim to satisfy three criteria, those concerning discoid rash, hematologic disorder, and antinuclear antibody.

5. Synopsis of Lupus as an Appropriate Diagnosis

The Vaccine Act recognizes that petitioners may establish their claims by submitting either “medical records or . . . medical opinion.” 42 U.S.C. § 300aa-13(a). Here, neither the medical records nor the medical opinions support a finding that Mr. D’Angiolini suffers from lupus.

The medical records contain the evaluations of many doctors who treated Mr. D’Angiolini. Although some doctors (notably, Doctors Bray, Hanson, and Galatro) indicated that Mr. D’Angiolini suffered from SLE, other doctors did not agree with this assessment. Among all the treating doctors, the doctor whose opinion was the strongest is Dr. Vasey. Dr. Vasey stated that Mr. D’Angiolini did not suffer from lupus. His opinion, as explained above, is given the most weight because he was capable of diagnosing lupus and had more than a decade to see signs and symptoms of lupus.

The reasons Dr. Vasey gave for not diagnosing Mr. D’Angiolini as having lupus, such as the lack of a malar rash and the lack of a positive ANA, effectively undercut the opinion presented by Dr. Shoenfeld. To support a lupus diagnosis for Mr. D’Angiolini, Dr. Shoenfeld stretched and pulled the diagnostic criteria well past a reasonable point. For example, Dr. Shoenfeld presented no basis for saying that cardiomyopathy qualifies as pericarditis and he presented no basis for saying that cognitive impairments qualify as psychosis. Ultimately, Mr. D’Angiolini’s efforts to fit within the lupus criteria are not persuasive.

B. Althen Analysis

The finding that Mr. D’Angiolini did not suffer from lupus essentially makes any examination of the Althen prongs unnecessary. See Lombardi, 656 F.3d at 1352. While as an abstract matter, there is sufficient evidence to determine whether Mr. D’Angiolini has established, by a preponderant evidence, that the hepatitis B vaccine can cause lupus (the first prong of Althen), there is no reason to engage in an exercise that would not affect the outcome of Mr. D’Angiolini’s case.

If a special master can determine that a petitioner did not suffer the injury that she claims was caused by the vaccine, there is no reason why the special master should be required to undertake and answer the separate (and frequently more difficult) question whether there is a medical theory, supported by “reputable medical or scientific explanation,” by which a vaccine can cause the kind of injury that the petitioner claims to have suffered.

Hibbard v. Sec'y of Health and Human Servs., 698 F.3d 1355, 1365 (Fed. Cir. 2012).

Even if it were found that Mr. D'Angiolini has met his burden on prong 1, his case would falter on prong 2. Since he does not suffer from lupus, all the evidence that he submitted in regard to "a logical sequence of cause and effect" connecting the hepatitis B vaccinations to his lupus is now irrelevant. Similarly, Mr. D'Angiolini cannot establish the third prong of Althen, which concerns temporality. Under this prong, Mr. D'Angiolini is required to establish that his lupus arose in an appropriate temporal proximity to the vaccination. But, this inquiry would be nonsensical because Mr. D'Angiolini has not established the predicate for this analysis, that he has lupus.

VIII. ASIA

Mr. D'Angiolini's final claim is that he suffered from an entity called Autoimmune Syndrome Induced by Adjuvant, sometimes known by its acronym ASIA. As explained in section A, Dr. Shoenfeld's experience in litigation helped him originate this entity. But, the criteria Dr. Shoenfeld has proposed are both vague and evolving as demonstrated in section B. Thus, for the reasons given in section C, Mr. D'Angiolini cannot receive compensation for this entity.

A. Origins

Dr. Shoenfeld is one of the initial proponents of ASIA and his experience contributed to the genesis of ASIA. Dr. Shoenfeld's background, as previously described, is extensive. He is listed as an author for more than 1500 articles published in peer-reviewed journals. Most of these have discussed some aspect of immunology and a sizeable number are about auto-immunity. In addition to his own writing, Dr. Shoenfeld has reviewed manuscripts submitted to prestigious journals as a peer-reviewer and as an editor. Dr. Shoenfeld has organized and lectured at conferences. Exhibit 85. Dr. Shoenfeld has reviewed Vaccine Program cases in which petitioners claimed that a vaccine injured them since at least 2006. See Sabella v. Sec'y of Health & Human Servs., No. 02-1627V, 2008 WL 4426040, at *23 (describing Dr. Shoenfeld's participation), mot. for review denied in part and granted in part, 86 Fed. Cl. 201 (2009). This experience gives Dr. Shoenfeld a perspective shared by few, if any, doctors.

In Dr. Shoenfeld's account, his work as an expert witness sparked his conceptualization of ASIA. In one case, the petitioner was exposed to a vaccine

and silicone. A question was whether either the vaccine or the silicone could have caused the petitioner's disease. Dr. Shoenfeld's insight was that in causing the disease, the vaccine and silicone could have worked synergistically. Tr. 996-97. Dr. Shoenfeld saw "two etiologies . . . caus[ing] a very common syndrome." Id. at 997. Dr. Shoenfeld also connected this etiology with the Gulf War Syndrome. Id. at 814-15, 996.

After Dr. Shoenfeld began configuring this syndrome, he retrospectively recognized other authors had reported findings consistent with ASIA, although these other authors had not used the same terminology. For example, to Dr. Shoenfeld, another manifestation of ASIA was the macrophage myofasciitis syndrome described by Dr. Gherardi. Tr. 814; see also Tr. 775 (Dr. Grotto "envisioned the ASIA syndrome before [Dr. Shoenfeld] dreamt about it").

B. Criteria

In his first article, Dr. Shoenfeld proposed the diagnostic criteria:

Major Criteria:

- Exposure to an external stimuli (infection, vaccine, silicone. adjuvant) prior to clinical manifestations.
- The appearance of 'typical' clinical manifestations:
 - Myalgia, Myositis or muscle weakness
 - Arthralgia and/or arthritis
 - Chronic fatigue, un-refreshing sleep or sleep disturbances
 - Neurological manifestations (especially associated with demyelination)
- Cognitive impairment, memory loss
- Pyrexia, dry mouth
- Removal of inciting agent induces improvement
- Typical biopsy of involved organs

Minor Criteria:

- The appearance of autoantibodies or antibodies directed at the suspected adjuvant
- Other clinical manifestations (i.e. irritable bowel syn.)
- Specific HLA (i.e. HLA DRB1,HLA DQB1)

- Evolvement of an autoimmune disease (i.e. MS, SSc)

Exhibit 88 (Yehuda Shoenfeld and Nancy Agmon-Levin, 'ASIA' – Autoimmune/inflammatory syndrome induced by adjuvants, 36(1) J. Autoimmunity 1 (2011)) at 4. On cross-examination, Dr. Shoenfeld was asked to explain these factors further.

For the first major criterion, Dr. Shoenfeld was open to expanding the list of external stimuli beyond the four common external stimuli listed in the article. "There might be additional stimuli which we still did not define." Tr. 905.

The second major criterion, "'typical' clinical manifestations" includes four signs or symptoms. Dr. Shoenfeld stated that a single episode of muscle weakness is sufficient to satisfy the criterion. Id. The types of neurological manifestations that are part of ASIA are numerous, including problems "from epilepsy to paresthesias." Tr. 906. Neurological problems stand in contrast to psychological problems, such as depression and obsessive-compulsive disorder, that do not fall within the ASIA criteria. Tr. 907.

Dr. Shoenfeld addressed the minor criteria as well. For the appearance of autoantibodies, Dr. Shoenfeld stated that "any autoantibodies" may appear in patients with ASIA. Tr. 920.

This initial paper did not specify how the criteria related to the diagnosis. For example, it was not clear whether a person needed to satisfy one, two, three or four of the major criteria for a diagnosis of ASIA. See exhibit 88; see also exhibit A (Dr. Lightfoot report) at 17. In a later paper, Dr. Shoenfeld wrote "to diagnose ASIA, fulfillment of either two major or one major and two minor criteria is required." Exhibit 189A (Y. Zafir et al., Autoimmunity following Hepatitis B vaccine as part of the spectrum of 'Autoimmune (Auto-inflammatory) Syndrome induced by Adjuvants' (ASIA): analysis of 93 cases, 21 Lupus 146 (2012)) at 150; accord Tr. 925-26.

In the context of testifying about the criteria, Dr. Shoenfeld asserted that "in about a year or two when we will revise all the criteri[a], . . . we will add many details . . . when we accumulate more experience and more cases." Tr. 920; accord Tr. 1471 (Dr. Shoenfeld: "we are each time examining ourselves. . . . We may add, we may detract, and so forth."). Dr. Lightfoot, too, anticipated that the criteria would need revision. To Dr. Lightfoot, "this was an initial attempt to sort of corral this concept and start to work on developing the criteria, but I don't think this

criteria set is sharp and crisp enough to say, okay, now we can really tell this syndrome from normal people.” Tr. 1181.

Dr. Lightfoot pointed to many examples of where he saw a lack of precision in the proposed diagnostic criteria. A recurring problem, in Dr. Lightfoot’s view, is that the criteria “are sufficiently ill-defined currently that it makes it very difficult to sort of make the diagnosis.” Tr. 1174. For example, both arthralgias (joint pain) and myalgias (muscle pain) are subjective symptoms about which many people complain. Tr. 1174-75. Another example is that virtually everyone in this country has received a vaccine. Thus, this factor does not help discriminate people with the disease. Tr. 1178.

To defend ASIA, Dr. Shoenfeld submitted a special issue of the journal Lupus that was devoted to ASIA. Exhibits 156-73. The editor of Lupus is Graham Hughes, a preeminent lupus rheumatologist in the United Kingdom. Tr. 1170. Dr. Hughes’s assessment of ASIA is ambiguous. With respect to a possible causal connection between the injection of foreign substances (such as vaccines and silicone) and the development of “‘auto-immune’-like syndromes,” Dr. Hughes wrote:

Professor Shoenfeld brings together compelling evidence for such a link. Whether through the adjuvant effects of aluminum (a component of many vaccines including flu vaccine) or from leaked silicone, there is now plausible evidence that in some individuals (perhaps those with a ‘predisposed’ auto-immune genetic background) there is a real possibility that the ASIA syndrome (Shoenfeld’s syndrome) is a genuine entity.

Exhibit 156 at 3. The progression in terminology from “compelling evidence” to “plausible evidence” to “real possibility” suggests that Dr. Hughes’s views are inchoate.

In addition to the special issue of Lupus, to validate his criteria, Dr. Shoenfeld relied upon one of his later studies involving 93 patients. Tr. 926-27, 1470. These patients were drawn from a larger population all of whom claimed that a vaccine harmed them and sought assistance from an attorney in seeking

compensation. Exhibit 189A (Zafir) at 146. The authors, including Dr. Shoenfeld, found that most of these people satisfied the ASIA criteria.⁷²

Dr. Lightfoot maintained that the process used in the Zafir article did not actually validate the ASIA criteria. He stated “validation does not mean taking all the patients attorneys have referred to you for an opinion, for example, and seeing if they meet the data set.” Tr. 1178. Instead, a proper validation would involve obtaining a “random sample of the population at large.” Tr. 1177-78. Obtaining “clean” epidemiological data would, Dr. Lightfoot admits, be a “daunting . . . task,” but one that is necessary. *Id.* Notably, Dr. Vasey, who seems to have the same outlook as Dr. Shoenfeld on many issues, also indicated that ASIA is “a new and novel concept that, you know, really should be tested out logically.” Tr. 1555.⁷³

C. Assessment

Dr. Shoenfeld has not made a persuasive case that ASIA is a legitimate and generally accepted medical condition. There is no ICD-9 code for ASIA. Tr. 927.⁷⁴ The diagnostic criteria, as Dr. Lightfoot credibly opined, cannot separate people with the disease from people without the disease.

Like Dr. Vasey, Dr. Lightfoot stated that “the ASIA syndrome as a concept is a very interesting hypothesis that needs to be developed.” Tr. 1175. Dr. Shoenfeld is working to refine the diagnostic criteria.⁷⁵ The potential evolution in

⁷² For example, 100 percent were exposed to an external stimulant, a vaccine, before they developed a disease. Exhibit 189A at 149 (table 3).

⁷³ Although the transcript states “tested out logically,” it is possible that Dr. Vasey actually stated “tested epidemiologically.” Regardless of the exact choice of words, Dr. Vasey’s point is the same. ASIA requires confirmation.

⁷⁴ For information about ICD-9, see *Koehn v. Sec’y of Health & Human Servs.*, 11-355V, 2013 WL 3214877, at *5 (Fed. Cl. May 30, 2013)(description of ICD-9 codes and their application for the purposes of treatment and research), mot. for review denied, (Fed. Cl. Dec. 3, 2013).

⁷⁵ Since millions of infants are vaccinated in their first year of life, a discussion about the medically appropriate temporal interval between exposure to the foreign substance and the onset of disease may be instructive. Dr. Shoenfeld’s opinion was that there is no amount of time that is too long. Tr. 917.

diagnostic criteria is reminiscent of the evolution in diagnostic criteria for chronic fatigue syndrome. See section VI.B.1 above. After further refinement, ASIA may be shown to be a “new avenue” in clinical medicine to which Dr. Hughes alluded. Exhibit 156.

The observation that ASIA does not have sufficient current support to be a reliable basis for compensation in the Vaccine Program is not intended as a criticism of Dr. Shoenfeld. The connection between scientific hypotheses and legal evidence was discussed by the Court of Appeals for the Sixth Circuit in a case involving the opinion of an expert who wanted to present a new theory to explain how exposure to welding materials caused Parkinson’s disease. The Sixth Circuit reversed the district court’s admission of the evidence, reasoning:

The sort of hypothesis Dr. Carlini presented can play a valuable role both in medicine, where, if the costs of action are low, doctors may want to act on hypotheses without further support, and in science generally, where all discoveries start as untested hypotheses. From this perspective, criticizing Dr. Carlini’s hypothesis for being speculative would be like criticizing a sapling for being short. Some hypotheses become scientific theories and others do not.

But that is not the issue. The issue is the reliability of his opinion from a legal perspective. And what science treats as a useful but untested hypothesis the law should generally treat as inadmissible speculation. As the Supreme Court has explained, “[t]he scientific project is advanced by broad and wide-ranging considerations of a multitude of hypotheses, for those that are incorrect will eventually be shown to be so.... Conjectures ... are of little use, however, in the project of reaching a quick, final, and binding legal judgment-often of great consequence-about a particular set of events in the past.” Daubert, 509 U.S. at 597.

Tamraz v. Lincoln Elec. Co., 620 F.3d 665, 677 (6th Cir. 2010). So it is with Dr. Shoenfeld’s ASIA hypothesis. It is like a sapling. After development and maturation, the idea of ASIA may be considered a reliable construct. However, the

evidence in Mr. D'Angiolini's case indicates that that day will come, if it arrives at all, in future.⁷⁶

Mr. D'Angiolini cannot receive compensation based upon his allegation that he suffers from ASIA. It is not generally accepted in the medical community and its diagnostic criteria do not differentiate between healthy and ill people. In short, Mr. D'Angiolini has failed to establish that Dr. Shoenfeld's opinion regarding ASIA meets the minimum threshold for reliability. See Moberly, 592 F.3d at 1324 (stating that special masters have the responsibility to evaluate the reliability of an expert's testimony); Vaccine Rule 8(c) (directing special masters to decide cases based upon all relevant and reliable evidence).

IX. Conclusion

Mr. D'Angiolini presents a sympathetic and complex picture. Before he was vaccinated, he was receiving assistance from a psychiatrist and psychologist for relatively serious issues. But, he was functioning well enough to hold a full-time job as a mental health technician and to work part-time as a music instructor. After receiving two doses of the hepatitis B vaccine, he continued to fulfill his professional obligations. But, his employment stopped after the third dose of the hepatitis B vaccine in 1997.

Mr. D'Angiolini claims that the hepatitis B vaccinations caused the change in his employment and all the other changes in his life and health. For his medical problems, Mr. D'Angiolini has consulted numerous doctors. The doctors have not figured out what is wrong with him. See exhibit 37 at 21 (Dr. Gorensek: "the patient had so many evaluations, so many differing opinions, that there is no one consistent opinion which makes it more suspicious that there really is not any significant opinion").

Although in this litigation Mr. D'Angiolini puts forward an allergy, a syndrome, a disease (lupus), and a newly proposed entity (ASIA), he has failed to establish persuasively that he suffers from any of them. Without a predicate

⁷⁶ For examples of instances in which a court barred testimony about a purported new diagnostic entity, see Kropp v. Maine School Admin. Union #44, 471 F.Supp.2d 175 (D. Me. 2007) (allergy to phenol as a specific example of multiple chemical sensitivity) and Gabbard v. Linn-Benton Housing Auth., 219 F.Supp.2d 1130 (D. Or. 2002) (multiple chemical sensitivity).

showing that a particular disorder afflicts him, Mr. D'Angiolini cannot receive compensation in the Vaccine Program.

The Clerk's Office is instructed to enter judgment in accord with this decision unless a motion for review is filed.

IT IS SO ORDERED.

s/ Christian J. Moran
Christian J. Moran
Special Master

Appendix A – Fukuda Criteria

Taken from: Keiji Fukuda et al., The Chronic Fatigue Syndrome: A Comprehensive Approach to Its Definition and Study, 121 Ann. Intern. Med. 953 (1994) (citations omitted throughout).

Guidelines for the Clinical Evaluation and Study of the Chronic Fatigue Syndrome and Other Illnesses Associated with Unexplained Chronic Fatigue

Definition and Clinical Evaluation of Prolonged Fatigue and Chronic Fatigue

Prolonged fatigue is defined as self-reported, persistent fatigue lasting 1 month or longer. Chronic fatigue is defined as self-reported persistent or relapsing fatigue lasting 6 or more consecutive months.

The presence of prolonged or chronic fatigue requires clinical evaluation to identify underlying or contributing conditions that require treatment. Further diagnosis or classification of chronic fatigue cases cannot be made without such an evaluation.

The following items should be included in the clinical evaluation.

1. A thorough history that covers medical and psychosocial circumstances at the onset of fatigue; depression or other psychiatric disorders; episodes of medically unexplained symptoms; alcohol or other substance abuse; and current use of prescription and over-the-counter medications and food supplements.
2. A mental status examination to identify abnormalities in mood, intellectual function, memory, and personality. Particular attention should be directed toward current symptoms of depression or anxiety, self-destructive thoughts, and observable signs such as psychomotor retardation. Evidence of a psychiatric or neurologic disorder requires that an appropriate psychiatric, psychological, or neurologic evaluation be done.
3. A thorough physical examination.
4. A minimum battery of laboratory screening tests including complete blood count with leukocyte differential; erythrocyte sedimentation rate; serum levels of alanine aminotransferase, total protein, albumin, globulin, alkaline phosphatase, calcium, phosphorus, glucose, blood urea nitrogen, electrolytes, and creatinine; determination of thyroid-stimulating hormone; and urinalysis.

Routinely doing other screening tests for all patients has no known value. However, further tests may be indicated on an individual basis to confirm or exclude another diagnosis, such as multiple sclerosis. In these cases, additional tests or procedures should be done according to accepted clinical standards.

The use of tests to diagnose the chronic fatigue syndrome (rather than to exclude other diagnostic possibilities) should be done only in the setting of protocol-based research. The fact that such

tests are investigational and do not aid in diagnosis or management should be explained to the patient.

In clinical practice, no additional tests, including laboratory tests and neuroimaging studies, can be recommended for the specific purpose of diagnosing the chronic fatigue syndrome. Tests should be directed toward confirming or excluding other etiologic possibilities. Examples of specific tests that do not confirm or exclude the diagnosis of the chronic fatigue syndrome include serologic tests for Epstein-Barr virus, retroviruses, human herpesvirus 6, enteroviruses, and *Candida albicans*; tests of immunologic function, including cell population and function studies; and imaging studies, including magnetic resonance imaging scans and radionuclide scans (such as single-photon emission computed tomography and positron emission tomography) of the head.

Conditions That Explain Chronic Fatigue

The following conditions exclude a patient from the diagnosis of unexplained chronic fatigue.

1. Any active medical condition that may explain the presence of chronic fatigue, such as untreated hypothyroidism, sleep apnea, and narcolepsy, and iatrogenic conditions such as side effects of medication.
2. Any previously diagnosed medical condition whose resolution has not been documented beyond reasonable clinical doubt and whose continued activity may explain the chronic fatiguing illness. Such conditions may include previously treated malignancies and unresolved cases of hepatitis B or C virus infection.
3. Any past or current diagnosis of a major depressive disorder with psychotic or melancholic features; bipolar affective disorders; schizophrenia of any subtype; delusional disorders of any subtype; dementias of any subtype; anorexia nervosa; or bulimia nervosa.
4. Alcohol or other substance abuse within 2 years before the onset of the chronic fatigue and at any time afterward.
5. Severe obesity as defined by a body mass index [body mass index = weight in kilograms/(height in meters)²] equal to or greater than 45.

Any unexplained physical examination finding or laboratory or imaging test abnormality that strongly suggests the presence of an exclusionary condition must be resolved before further classification.

Conditions That Do Not Adequately Explain Chronic Fatigue

The following conditions do not exclude a patient from the diagnosis of unexplained chronic fatigue.

1. Any condition defined primarily by symptoms that cannot be confirmed by diagnostic laboratory tests, including fibromyalgia, anxiety disorders, somatoform disorders,

nonpsychotic or nonmelancholic depression, neurasthenia, and multiple chemical sensitivity disorder.

2. Any condition under specific treatment sufficient to alleviate all symptoms related to that condition and for which the adequacy of treatment has been documented. Such conditions include hypothyroidism for which the adequacy of replacement hormone has been verified by normal thyroid-stimulating hormone levels or asthma in which the adequacy of treatment has been determined by pulmonary function and other testing.
3. Any condition, such as Lyme disease or syphilis, that was treated with definitive therapy before development of chronic symptomatic sequelae.
4. Any isolated and unexplained physical examination finding or laboratory or imaging test abnormality that is insufficient to strongly suggest the existence of an exclusionary condition. Such conditions include an elevated antinuclear antibody titer that is inadequate to strongly support a diagnosis of a discrete connective tissue disorder without other laboratory or clinical evidence.

Major Classification Categories: Chronic Fatigue Syndrome and Idiopathic Chronic Fatigue

Clinically evaluated, unexplained cases of chronic fatigue can be separated into either the chronic fatigue syndrome or idiopathic chronic fatigue on the basis of the following criteria.

A case of the chronic fatigue syndrome is defined by the presence of the following:

- 1) clinically evaluated, unexplained, persistent or relapsing chronic fatigue that is of new or definite onset (has not been lifelong); is not the result of ongoing exertion; is not substantially alleviated by rest; and results in substantial reduction in previous levels of occupational, educational, social, or personal activities; and
- 2) the concurrent occurrence of four or more of the following symptoms, all of which must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue: self-reported impairment in short-term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social, or personal activities; sore throat; tender cervical or axillary lymph nodes; muscle pain, multijoint pain without joint swelling or redness; headaches of a new type, pattern, or severity; unrefreshing sleep; and postexertional malaise lasting more than 24 hours.

The method used (for example, a predetermined checklist developed by the investigator or spontaneous reporting by the study participant) to establish the presence of these and any other symptoms should be specified.

A case of idiopathic chronic fatigue is defined as clinically evaluated, unexplained chronic fatigue that fails to meet criteria for the chronic fatigue syndrome. The reasons for failing to meet the criteria should be specified.

Appendix B – Tan Criteria

Taken from: Eng M. Tan et al., The 1982 Revised Criteria for the Classification of Systemic Lupus Erythematosus, 25 Arthritis Rheumatism 11 (1982)).

The 1982 revised criteria for classification of systemic lupus erythematosus*

1. Malar rash
Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash
Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity
Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers
Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5. Arthritis
Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis
 - a) Pleuritis - convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion, or
 - b) Pericarditis- documented by ECG or rub or evidence of pericardial effusion
7. Renal disorder
 - a) Persistent proteinuria greater than 0.5 grams per day or greater than 3+ if quantitation not performed, or
 - b) Cellular casts - may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder
 - a) Seizures--in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance, or
 - b) Psychosis--in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic disorder
 - a) Hemolytic anemia- with reticulocytosis, or

- b) Leukopenia - less than $4,000/\text{mm}^3$ total on 2 or more occasions, or
- c) Lymphopenia - less than $1,500/\text{mm}^3$ on 2 or more occasions, or
- d) Thrombocytopenia - less than $100,000/\text{mm}^3$ in the absence of offending drugs

10. Immunologic disorder

- a) Positive LE cell preparation, or
- b) Anti-DNA: antibody to native DNA in abnormal titer, or
- c) Anti-Sm: presence of antibody to Sm nuclear antigen, or
- d) False positive serologic test for syphilis known to be positive for at least 6 months and confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test

11. Antinuclear antibody

An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

* The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person shall be said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.